Ocular Diseases

Chapter 3

Eyes on the Liver: Ocular manifestations of Liver Diseases

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1. Introduction

The liver plays a crucial role in various functions of the body, including gluconeogenesis, detoxification, metabolism, energy storage, drug clearance, and fat absorption through the production and excretion of bile. Several disorders that affect the liver also demonstrate ocular findings. This can be seen in metabolic diseases where a toxic metabolite accumulates and causes subsequent visual impairment as well as abnormal ophthalmologic exam findings. Additionally, impaired bile excretion may lead to visually abnormal features on exam as well as impaired fat absorption which deprives the body of vitamin A, a necessary vitamin for ocular health and function. Recognizing the association between disorders of the eye and the liver is beneficial in establishing and/or confirming a diagnosis, as well as understanding the proper management for these nuanced diseases.

Disorders of Cholesterol Dysregulation

Liver disease is often associated with disordered cholesterol metabolism and may result in hypercholesterolemia. When serum cholesterol levels are elevated, this can result in accumulation of cholesterol-rich substances in the body and most notably the skin. These deposits, called xanthomas, typically appear flesh-colored, may be hard, and are often numerous throughout the body [1]. Lipid deposits of cholesterol found specifically on the eyelids along the medial canthal regions are termed xanthelasma. Xanthelasma appear as soft, yellow plaques **(Figure 1)**, and may be seen in healthy individuals as well as those with cholestasis and hypercholesterolemia [2]. These plaques are benign and typically do not require treatment

unless there is related visual impairment or per patient cosmetic preference [1]. Lipid deposits may also present as arcus senilis, which are gray or white appearing rings located peripherally on the cornea. Similar to xanthomas and xanthelasmas, these findings may occur in liver disease but are nonspecific, potentially due to other causes of lipid dysregulation [3].

Figure 1: Xanthelasma.

Conjunctival Icterus

Yellow discoloration of the eyes may clinically be one of the first detected symptoms of liver disease **(Figure 2)**. Icterus may be appreciated on exam when serum bilirubin levels exceed 2 mg/dL and is best appreciated with serum bilirubin is above 3 mg/dL [2,4]. While often described as "scleral icterus," the conjunctiva is more precisely the area affected by elevated bilirubin levels as opposed to the sclera [2]. High elastin content of the conjunctiva binds with high affinity to bilirubin, resulting in the bilirubin accumulation and clinical finding of icterus. Yellowing of the skin also often occurs in the setting of hyperbilirubinemia, and when yellowing of the skin occurs with sparing of the conjunctiva, alternative diagnosis such as carotenoderma due to excessive consumption of carotene-rich foods should be considered [4]. Additionally, even when correctly identified as icterus, the finding may alternatively be due to indirect hyperbilirubinemia which does not stem from cholestasis, but rather due to hemolysis or Gilbert's syndrome, a benign genetic disorder affecting bilirubin metabolism [4].

Figure 2: Conjunctival Icterus.

Congenital and Neonatal Infections

Congenital intrauterine infections result in various systemic manifestations often caused either by a direct toxic effect resulting in inflammation and necrosis, or via teratogenic effect if contracted in the first trimester. Among the clinically significant congenital infections, *Toxo-*

plasma gondii, rubella, cytomegalovirus, Herpes Simplex Virus (HSV), and Treponema pallidum often have notable hepatic and ophthalmologic effects [5]. *T. gondii* can cause cataracts and microcornea in the anterior segment of the eye, as well as chorioretinal scarring, retinitis, retinal detachment, and optic nerve atrophy [6]. Generally, with antibiotic treatment, namely pyrimethamine-sulfonamides, affected children tend to experience favorable visual outcomes although visual impairment may persist in those with severe ocular disease [7]. In congenital rubella, affected patients may present with cataracts, salt and pepper retinopathy, glaucoma, and optic nerve atrophy. Congenital cytomegalovirus may cause corneal scarring, cataracts, chorioretinitis, optic nerve atrophy, optic nerve hypoplasia, and strabismus [6]. In the newborn, HSV most often is acquired during passage through the birth canal and is usually more accurately considered a neonatal infection, although true congenital infection may occur in about 4% of cases in the newborn period [5]. Ocular findings are a hallmark in neonatal HSV specifically among the Skin, Eyes, Mouth form of the disease, and include conjunctivitis, keratitis, cataracts, retinitis, chorioretinitis, and optic nerve atrophy, amongst other findings. Treponema pallidum when acquired congenitally may lead to corneal opacification and scarring, cataracts, Argyll-Robison pupil, uveitis, salt and pepper retinopathy, glaucoma, optic nerve atrophy, and eyelid condyloma lata [6].

These congenital infections may also cause liver injury as demonstrated by lab abnormalities such as cholestasis and transaminitis as well as exam findings such as hepatomegaly. Thus, careful consideration of ocular abnormalities may be helpful in these cases when considering the possible diagnoses of conjugated hyperbilirubinemia in the infant and neonate. Ophthalmologic findings are typically associated with abnormalities of the central nervous system in cases of congenital infection, but do not often associate with long term visual impairment [6].

Primary Biliary Cholangitis

Primary biliary cholangitis is a cholestatic liver disease that occurs due to autoimmune mediated intrahepatic bile duct destruction. As many as 73% of patients with primary biliary cholangitis experience extra-intestinal manifestations associated with their disease. Sjögren's syndrome is the most common extra-intestinal manifestation of primary biliary cholangitis, and is itself an autoimmune disease affecting exocrine glands which can occur in isolation or in association with other autoimmune conditions [8,9]. Lymphocytic infiltration of lacrimal and salivary glands leads to symptoms of dry mouth and dry eyes which are the predominant symptoms of this syndrome. Sjögren's syndrome is diagnosed based on clinical history, autoimmune markers, and histology. Management of Sjögren's syndrome is primarily supportive with use of artificial tears for the treatment of xerostomia [8].

Hepatitis C Virus Infection

Sicca syndrome, similar to Sjögren syndrome, presents with dry mouth and eyes due to lymphocytic infiltrates in lachrymal and salivary glands. The literature has demonstrated association between Hepatitis C Virus (HCV) infection and the development of sicca syndrome in adults, although mechanisms remain unclear [6,10]. Estimates propose around 20-30% of patients with hepatitis C develop these ocular and salivary symptoms. However, the mechanism and histology appear distinct from Sjogren's syndrome, as salivary gland histology and autoimmune markers are not consistent among Sjogren's syndrome and HCV related sicca syndrome [11]. Conjunctival inflammation has been demonstrated to occur in response to hepatitis C core proteins and NS3 antigens which may contribute to this dry eye condition [12]. It also has been noted that patients with chronic HCV infections with advanced liver disease, such as advanced stages of hepatic fibrosis, had associated worse severity of ocular surface damage and significant signs of dry eyes [13].

Xeropthalmia

Vitamin A deficiency may result in a constellation of ophthalmologic symptoms, specifically conjunctival and corneal xerosis, Bitot's spots, keratomalacia, night blindness, and retinopathy, which collectively are termed xeropthalmia [14]. Vitamin A deficiency may occur as a result of insufficient consumption of vitamin A in one's diet, including in small children in settings with limited resources, as well as due to extremely limited diet due to picky eating behaviors [14,15]. Alternatively, defective vitamin A metabolism may occur in the setting of chronic liver disease and similarly result in xeropthalmia. In the setting of chronic liver disease and cholestasis, impaired excretion of bile leads to fat malabsorption and subsequently deficiencies in fat soluble vitamins A, D, E, and K [14]. Furthermore, hepatic stellate cells which store vitamin A are damages in the setting of cirrhosis, thus further depleting vitamin A stores [1].

Vitamin A is crucial in the functioning of the rhodopsin system of rod cells. Thus, deficiency of vitamin A results in nyctalopia, or impaired vision in dim light. This usually is the first symptom of xeropthalmia to develop. Conjunctival xerosis appears as a dull appearance of the conjunctiva due to altered composition of epithelial proteins and decreased mucin production. Corneal xerosis presents as dry appearing cornea which initially may be superficial and reversible but ultimately may progress to keratomalacia, or corneal melting, resulting in permanent visual impairment. Bitot spots, also seen in vitamin A deficiency, are white-appearing raised patches on the palpebral conjunctiva resulting from built-up keratinized epithelial cells. Ultimately, structural changes in the retina may occur in severe, prolonged vitamin A deficiency, referred to as xerophthalmic fundus [14].

Unless xeropthalmia has progressed to a severe form, the ophthalmologic symptoms are

often reversible with vitamin A supplementation, ocular lubricants, and addressing any underlying contributing disease. In patients with chronic liver disease, high doses of oral vitamin A, such as 5000-15,000 IU daily may be used [1].

Alagille Syndrome

Alagille syndrome is an autosomal dominant disorder known to have variable penetrance, characterized by multisystem involvement including cholestasis, cardiac disease, skeletal findings, and ocular abnormalities. The syndrome occurs most often due to mutations in genes involved in the Notch signaling pathway, including *JAG1* and *NOTCH2* [6]. The vast majority of patients with Alagille syndrome, an estimated 95%, are diagnosed with a detectable pathogenic variant in *JAG1*. A much smaller portion, about 2.5% of patients diagnosed with Alagille syndrome, demonstrate a pathogenic variant in *NOTCH2* [16]. Interestingly, patients with this disorder demonstrate variable phenotypic penetrance with varying presentation and severity of affected systems even amongst patients with the same gene mutation. Of the organ systems involved, hepatic and cardiac involvement typically have the most significant effects on patient health and are most likely to have associated morbidity and/or mortality [6,16]. In fact, patients with Alagille syndrome may require liver transplantation in childhood due to bile duct paucity resulting in cholestasis. Additionally, some patients require extensive cardiac surgery to correct structural cardiac defects such as pulmonary artery hypoplasia or tetralogy of Fallot. The involvement of other organ systems additionally influences the clinical course of patients with Alagille syndrome and also may be pivotal in diagnosing this disease [16].

The most common ocular abnormality of Alagille syndrome is posterior embryotoxon as seen in **Figure 3**. This refers to an anomalous line at Schwalbe ring, which demarcates the corneal epithelium and uveal trabecular meshwork [16]. This is appreciated on slit lamp examination and unable to be detected by unassisted visual inspection [1]. Up to 95% of individuals with Alagille syndrome are found to have posterior embryotoxon [16]. This finding is not associated with visual impairment, and actually occurs in somewhere between 8-15% of individuals in the general population [17]. It is subsequently not diagnostic for Alagille syndrome, but is the most common ocular abnormality in this disease and can meaningfully contribute to diagnosis [16].

An additional ocular abnormality seen in Alagille syndrome is optic disc drusen, a condition caused by the accumulation of various substances in the optic nerve head [16,18,19]. These substances include calcium, amino acids, nucleic acids, and mucopolysaccharides and are detected on ophthalmoscopy [19]. Unlike posterior embryotoxon, optic drusen frequently presents with visual field defects. This is typically a bilateral finding and can occur in 0.4-3.7% of the general population. Optic disc drusen is usually managed primarily via observation, but in cases of progressively worsening visual field defects, vasoactive therapy and surgical treat-

ment may be considered. Furthermore, if associated increased intraocular pressure is noted, therapy may be targeted toward lowering intraocular pressure [19].
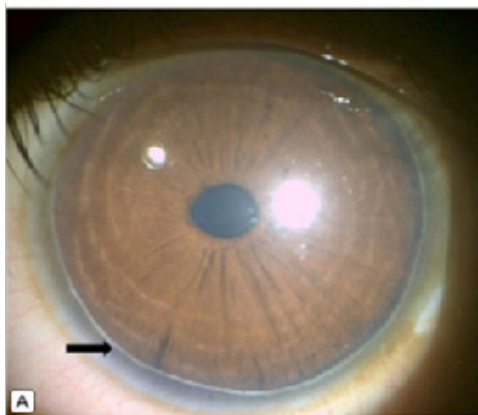

Figure 3: Posterior embryotoxon.

Wilson's Disease

Wilson's disease is a disorder of copper metabolism that results in various clinical signs and symptoms, including liver disease, neurological impairment, and psychiatric disease, and presents with distinct ocular findings that aid in diagnosis. It is a genetic disorder caused by mutations in the ATP7B gene, which encodes a protein involved in copper transport, subsequently resulting in increased copper deposits in various organs including the liver and brain. The majority of patients begin experiencing symptoms of Wilson's disease in the second or third decade of life, often initially with neurologic symptoms, specifically dystonia or parkinsonism. Liver disease can present as a range of symptoms varying from chronic liver disease to acute liver failure [20].

Scoring systems which include incorporation of serum ceruloplasmin, urinary copper, and presence of neurologic symptoms, amongst other clinical data and features have been created with general acceptance by professional societies but currently there are no universal criteria for diagnosing Wilson's disease [20]. Per the American Association for the Study of Liver Disease (AASLD) practice guidelines, the presence or absence of Kayser-Fleischer rings on slit lamp examination in the setting of unexplained liver disease functions in the diagnostic algorithm as one of the first features assessed to stratify likelihood of this diagnosis [21]. Thus, detection of this ocular finding is crucial in diagnosing this disease [20].

Kayser-Fleischer rings

Kayser-Fleischer rings demonstrate corneal copper deposition which results in a visible ring that appears to surround the iris **(Figure 4)**. Excess copper specifically accumulates on the inner surface of the cornea, starting at Schwalbe's line, and extends to the trabecular meshwork. Initially, this finding is only visible on slit lamp examination performed by an experienced provider, and may subtly begin developing superiorly before presenting inferiorly and subsequently circumferentially. In much later stages, the rings can be visualized with

the naked eye and most commonly appear bilaterally, and golden brown in color, but may alternatively appear greenish-yellow, red, green, or blue [22]. Up to 95% of patients presenting with neurologic symptoms of Wilson's disease have Kayser-Fleischer rings. Additionally, about half of patients with Wilson's disease who do not demonstrate neurologic symptoms also demonstrate this finding [23]. Vision is not impaired in patients with Kayser-Fleischer rings. Treatment of underlying Wilson's disease by copper chelation therapy will ultimately resolve the Kayser-Fleischer rings. Chelation with agents such as penicillamine and trientine bind the excess copper to facilitate urinary excretion [22]. Sunflower cataracts may also be seen in Wilson's disease and result from copper deposition in the lens [23]. Similar to Kayser-Fleisher rings, sunflower cataracts do not result in visual impairment [22]. However, they are only visualized via slit lamp examination [23].

Figure 4: Kayser-Fleischer rings.

Galactosemia

Classic galactosemia (type1) occurs due to the impairment of galactose-1-phosphate uridylyltransferase (GALT), an enzyme crucial in galactose metabolism [1]. This disorder is inherited in an autosomal recessive manner and results in excess galactose-1-phosphate. This results in multi-organ manifestations including liver dysfunction, rental tubular disease, failure to thrive, cataracts, and increased risk of *E. coli* sepsis. Galactosemia is treated by dietary restriction of lactose and galactose, and when this disease is detected early, dietary intervention resolves risks of these complications [24].

In the absence of GALT, galactose-1-phosphate undergoes metabolism to various products including galactitol and galactonate [24]. The metabolite galactitol subsequently accumulate intracellularly and when this occurs in the lens, it results in the clinical feature of cataracts. Newborns with classic galactosemia will often present with cataracts at birth which may be reversed if lactose and galactose restricted diet is initiated early [1,24].

A less severe form of galactosemia caused by galactokinase (GALK) deficiency (type 2 galactosemia) may progress gradually in contrast to classic galactosemia [1,24]. In this case, cataracts may still be present in infancy, but alternatively the patient may not be diagnosed until cataracts are detected in adulthood. Type 2 galactosemia is also treated with dietary restriction of lactose and galactose [24].

Lysosomal Storage Disorders

Various lysosomal storage disorders demonstrate abnormal ophthalmologic findings, specifically involving the retina. The lysosome is an organelle that functions to break down many compounds within the cell. Defects in lysosomal enzymes can lead to an excess of these products that were unable to be further metabolized, which may then be stored and deposited throughout the body leading to notable complications [25]. Among these diseases are Mucopolysaccharidoses (MPS), Niemann-Pick disease, GM_2 Gangliosidoses, and Gaucher disease.

Mucopolysaccharidoses

MPS are metabolic disorders caused by defective lysosomal enzymes responsible for breakdown of glycosaminoglycans (GAG). These disorders occur due to deposition of GAG both intracellularly and extracellularly and exist along a spectrum, with certain disorders resulting in early mortality within the first few months of life, and others allowing for normal life expectancy [26]. Clinically, features amongst this family of disorders include coarsened facial features, hepatosplenomegaly, skin thickening, and corneal clouding, attributable to the accumulation of the unprocessed GAG [1].

Severe forms of MPS include MPS I (Hurler syndrome), MPS II (Hunter syndrome), and MPS VI (Maroteaux-Lamy syndrome) and typically present early in life with cardiac, respiratory, or skeletal involvement. Amongst these forms of MPS, hepatosplenomegaly is most notable in MPS I (Hurler syndrome) and MPS II (Hunter syndrome). Abdominal distension caused by hepatosplenomegaly can result in hernias and limit lung expansion [27,28]. Even though deposition of GAG has been found on liver histology in these patients, liver dysfunction does not appear to complicate the course of this disease [26,27].

Corneal clouding classically presents in MPS I and MPS VI, as shown in **Figure 5**. This occurs due to deposition of dermatan sulphate in the cornea of these individuals as a result of impaired α-L-iduronidase in MPS I and N-acetylgalactosamine-4-sulfatase in MPS VI. Although case reports have described corneal clouding in MPS II, this is rare and usually the presence of corneal clouding excludes the diagnosis of MPS II [27]. In severe cases, corneal clouding in patients with MPS I and MPS VI can be treated with corneal transplant. As described below, patients with involvement of the retina and optic nerve may not experience improved vision despite corneal transplant [26].

Patients with severe forms of MPS I commonly also suffer from optic nerve involvement. GAG deposition in the dura and sclera surrounding the optic nerve may lead to nerve compression and eventual swelling and atrophy. Alternatively, patients with MPS often experience communicating hydrocephalus and subsequent raised intracranial pressure which may also result in optic disk swelling and nerve atrophy. Therefore, consideration of elevated ICP

should be included with optic disk evaluation in these cases [26].

Retinopathy, presenting as night blindness and impaired peripheral vision, can also occur in various forms of MPS, including specifically MPS II. This results from GAG accumulation in retinal pigment epithelial cells and photoreceptor matrix [29] and can be detected by abnormal electroretinogram (ERG). Clinically, corneal clouding may overshadow retinopathy thus delaying detection of this problem.
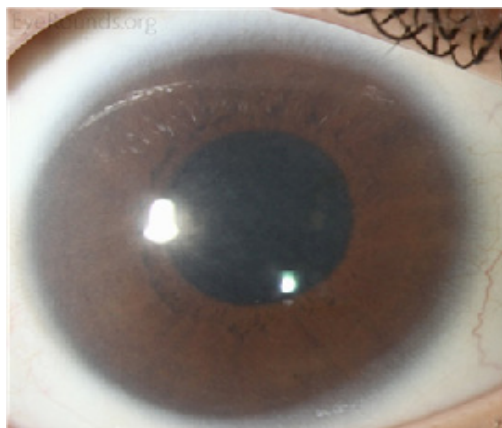

Figure 5: Corneal clouding.

Niemann-Pick Disease

This rare neurodegenerative disorder occurs due to impaired function of the enzyme sphingomyelinase which breaks down sphingomyelin. This lipid subsequently accumulates in multiple tissues, including the liver, spleen, lymph nodes, and brain, with significant clinical consequences [6]. Niemann-Pick disease type A is the most severe form and typically results in fatality in early childhood [25]. The most common presenting symptom is hepatosplenomegaly which may be detected around three months of age [6]. Some patients develop cholestatic liver disease and may progress to liver failure due to the liver injury caused by sphingomyelin deposition. Similarly, the brain becomes enlarged in the first year of life due to sphingomyelin accumulation, but subsequently atrophies [25]. In conjunction with various other lysosomal storage diseases, Niemann-Pick may present with the ophthalmologic finding of cherry-red macula. Retinal artery occlusion and subsequent retinal perfusion results in pale appearance of the retina. Foveal cells remain pigmented but surrounding ganglion cells are diseased, thus appearing white. The normally pigmented foveal cells surrounded by contrasting ganglion cells produce the finding of cherry-red macula shown in **Figure 6** [30].
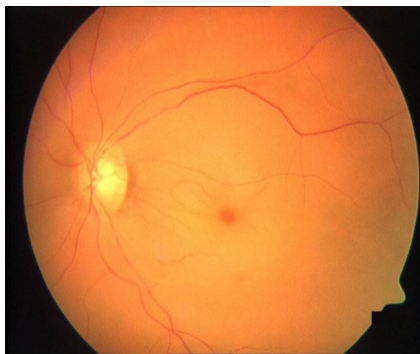
Figure 6: Cherry red macula.

GM$_2$ Gangliosidoses

GM^2 gangliosidosis disorders, including Tay-Sachs disease Sandhoff disease, are attributable to deficient β-hexosaminidase. Tay-Sachs is specifically caused by dysfunctional hexosaminidase A whereas Sandhoff disease occurs due to dysfunctional hexosaminidase A and hexosaminidase B. Those with Tay-Sachs and Sandhoff disease demonstrate the feature of cherry-red macula as noted above, also seen in Niemann-Pick disease. While various forms exist for both diseases, patients with severe forms of Tay-Sachs and Sandhoff disease are born without findings of the disease, but within the first year of life demonstrate significant clinical deterioration. Patients with Tay-Sachs specifically demonstrate psychomotor symptoms, seizures, and hypotonia. Parents may notice visual impairments as affected infants demonstrate worsening vision with many experiencing blindness. This disease is fatal by 3-5 years of age [25]. Those with Sandhoff disease may present similarly to patients with Tay-Sachs including neurologic findings of seizures, hypotonia, blindness, and psychomotor deficits. Patients with Tay-Sachs disease do not demonstrate hepatomegaly, while those with Sandhoff disease may demonstrate hepatosplenomegaly especially in infantile form when presenting before the age of six months [31].

Gaucher Disease

Gaucher disease is caused by deficiency of glucocerebrosidase and is the most common lysosomal storage disease. As a result of the enzyme deficiency, excess glucocerebroside is unable to be converted to ceramide and glucose and subsequently accumulates intracellularly. Various forms of Gaucher disease exist, representing varying degrees of glucocerebroside impairment which results in a spectrum of disease severity and presentation. Type 1 lacks primary CNS involvement and is typically diagnosed in early-to-mid adulthood. Patients with type 1 disease demonstrate hepatosplenomegaly, anemia, osseous abnormalities, and impaired growth [30]. Patients may have normal life expectancy, although they remain at increased risk of certain malignancies including multiple myeloma and hepatocellular carcinoma later in life. Patients with type 2 disease experience early infantile onset with severe CNS involvement. Certain neurologic findings such as cranial nerve or extrapyramidal tract deficits can present as early as birth. They progress to demonstrate hepatosplenomegaly, strabismus, ocular apraxia,

retroflexion of the head, hyperreflexia, and limb rigidity. Management is generally supportive; patients with type 2 Gaucher disease usually die within the first two years of life. Type 3 disease presents with neurologic symptoms but somewhat later in onset compared to type 2 disease, with symptoms beginning at a median age of 1 year of life. Common associated symptoms include abnormal saccadic eye movements, ataxia, seizures, and developmental delay. Enzyme replacement treatment can be considered in type 1 disease for management of various systemic effects of the disorder but does not provide neurologic benefit [25]. Deposition of metabolic byproducts, specifically in the retina, conjunctiva, and uvea, can result in visual deficits and impaired eye movement [30].

Mitochondrial Liver Disease

Within the cell, mitochondria create usable energy that the human body requires to function. Mitochondrial diseases that impair energy production via respiratory chain pathways often impact organs with high energy requirements, including the liver and the eyes [32]. Deoxyguanosine kinase (DGUOK) deficiency is a mitochondrial disorder that occurs due to a defect in the enzyme that contributes to nucleotide synthesis. This disorder can present in infancy with liver failure, developmental regression as well as ocular findings of rotary nystagmus or opsoclonus [33]. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD), another mitochondrial disorder, results from a dysfunctional enzyme involved in the metabolism of fatty acids. This disease may present with severe manifestations, including liver dysfunction, sudden death, and cardiomyopathy, or may have a less severe course which presents later in childhood. About half of patients with LCHAD are thought to also experience retinopathy and associated visual impairment [32, 34]. MPV17-related mitochondrial DNA maintenance defect is a rare disorder that usually presents in infancy with liver dysfunction progressing to failure as well as encephalopathy. Other systems are often affected, including gastrointestinal involvement and metabolic derangements, including hypoglycemia and lactic acidosis [35]. Ocular findings include retinopathy, nystagmus, and corneal abrasions/ulcerations [32, 35]. Pathogenic mutations in the gene encoding for mitochondrial DNA polymerase, POLG, can present on a spectrum of illness severity, including neonatal/infantile liver failure. Optic atrophy may also be seen in cases of POLG mutations [32].

Peroxisomal Disorders

Zellweger syndrome is caused by a defect enzyme trafficking to peroxisomes, which are the organelles responsible for degradation of very long chain and branched fatty acids. This disease is autosomal recessive and typically very severe and progressive in nature leading to death by the age of one year [36]. The cellular accumulation of fatty acids in many organs may result in distinct craniofacial findings, hepatomegaly, cholestasis, neurologic impairment, seizures, renal cysts, and ocular abnormalities [6]. Among the eye abnormalities, patients with

Zellweger syndrome experience severe posterior segment abnormalities, including loss of photoreceptors and reduced retinal pigment epithelium and ganglion cells. Optic nerve injury and demyelination may also occur. To varying extents, corneal clouding and cataracts may be present as well. Similar to Zellweger syndrome, neonatal adrenoleukodystrophy occurs as a result of impaired formation of peroxisomes and presents with similar findings. While this disease also presents in the neonatal period and results in early fatality, the presentation of Zellweger syndrome is classically more severe [36].

Congenital Hypopituitarism and Septo-optic Dysplasia

Congenital hypopituitarism occurs when a neonate demonstrates deficiency of at least one of the peptide hormones produced by the anterior pituitary, including growth hormone, thyroid stimulating hormone, and adrenocorticotropic hormone [6,37]. In the neonatal period, patients may present as hypotensive and critically ill. However, up to one-third of cases of congenital hypopituitarism may present initially with neonatal cholestasis. Patients may demonstrate conjugated hyperbilirubinemia with either low or normal GGT, hypoglycemia, and microphallus [6].

In some patients, congenital hypopituitarism presents as one feature of septo-optic dysplasia. Septo-optic dysplasia is classically characterized by the triad of hypopituitarism, optic nerve hypoplasia, and absence of the septum pellucidum and/or corpus callosum. Meeting two of these three features is sufficient for a diagnosis of septo-optic dysplasia, and somewhere between 30-47% of patients manifest all three findings. Causative factors have not been definitively determined, although genetic predisposition and environmental factors are thought to contributen [38]. Various genes heavily involved in embryologic development, including $HESX_1$, SOX_2/SOX_3, and OTX_2, have been suspected to contribute to the development of septo-optic dysplasia. While rare familiar cases have been noted, this disorder is generally sporadic. Epidemiological studies have demonstrated a correlation between this disorder and maternal age below 22 years [39].

Optic nerve hypoplasia itself speaks to the underdevelopment of the optic nerves and with findings of optic nerve hypoplasia shown in **Figure 7**. Optic nerve hypoplasia leading to visual impairment may be a common presenting symptom of septo-optic dysplasia, but as few as 23% of reported symptoms in this condition are associated with visuals defects. Indeed, some patients initially present with severe visual impairment with later progression of endocrinopathy. Others are primarily affected by other midline defects with significant neurologic implications, including seizures, cerebral palsy, and developmental delay. Additionally, isolated optic nerve hypoplasia without other features of septo-optic dysplasia is termed optic nerve hypoplasia syndrome with a distinct pathogenesis and course not involving other midline structures or endocrine abnormalities [38].

Clinically, the most common ocular sign of septo-optic dysplasia in the newborn is nystagmus, but often not determined to be pathologic until 3-6 months of life. Nystagmus patterns include univectorial, bivectorial, multivectorial, jerk and pendular nystagmus. Unilateral or bilateral optic nerve involvement may be present, with bilateral involvement suggesting more severe visual impairment [38]. Additional findings on ophthalmologic exam can provide helpful information regarding the presence or severity of optic nerve disease. Sluggish or absent pupillary response always serves as a poor prognosticator for visual acuity. On the other hand, normal response does not always convey reassuring visual acuity. Markers of abnormal visual axes, such as exam findings of esotropia, exotropia, and strabismus can be seen in optic nerve hypoplasia [40]. Strabismus may be appreciated by twelve months of life. Progressive vision loss is expected in many patients with septo-optic dysplasia with significant risk of blindness in over three-quarters of patients with bilateral optic nerve hypoplasia [38].

Direct video-ophthalmoscopy assessment is warranted for optic disk and optic nerve assessment, assessing for findings of small-appearing optic disc with associated pigmented ring as well as small optic nerve area. Additionally, disc tilting, abnormal nerve fiber layer, and tortuous retinal vessels may be present [40]. Due to subjectivity in measuring optic disc size, techniques to instead measure relative disc size have been proposed to standardized this measurement which may be particularly useful in young patients [41,40].

Optic nerve hypoplasia as a feature of septo-optic dysplasia does not have a definitive treatment. However, ophthalmologic features including amblyopia and refractive errors require monitoring and management as indicated, with ophthalmology follow-up on at least an annual basis [38, 40]. Use of eye patching and strabismus surgery have not demonstrated consistent evidence of utility in managing strabismus for these patients, and are therefore not universally recommended. Certain individuals, however, may benefit from these therapies, especially strabismus surgery if psychosocial factors contribute [40].

Figure 7: Optic nerve hypoplasia.

Familial Adenomatous Polyposis Syndrome

Familial adenomatous polyposis is an autosomal dominant condition which occurs due to mutations in the APC gene. Most often, this disease is inherited, but can occur as a result

of de novo mutations in 20-30% of cases. Patients with this condition suffer from numerous colorectal adenomas which, if left untreated, almost inevitably transform into invasive carcinoma, occurring at an average age of 40 years. Numerous extraintestinal manifestations of familial adenomatous polyposis syndrome exist, including gastric fundic gland polyps, congenital hypertrophy of retinal pigment epithelium (CHRPE), fibromas, fibromatosis, nasal angiofibromas, thyroid carcinoma, hepatoblastoma, brain tumors, and pancreatobiliary tumors [42]. The location of the mutation on the APC gene appears to correlate with disease severity as well as the presence of extraintestinal manifestations [43]. Management of propensity for colorectal cancer involves eventual colectomy. However, this does not avert risk for numerous extraintestinal manifestations, specifically other malignancies such as hepatoblastoma [42].

The most common extraintestinal manifestation in individuals with familial adenomatous polyposis is congenital hypertrophy of retinal pigment epithelium (CHRPE), occurring in about 90% of FAP patients. This is typically the earliest manifestation as well, and may even present in the newborn period. On exam, this is visualized as one or more darkly pigmented lesions with a halo in the retina, as shown in **Figure 8**. The lesions may take on various shapes, including circular, oval, or coffee bean, and also vary in size [42]. These lesions are benign, but notably contain focal malformations of the melanin granules which histologically resemble neoplasms [44]. Typically, there are no associated visual impairments [45]. Similar appearing lesions may be seen in 1.2-4.4% of the general population. However, when noted, these findings should raise suspicion for FAP given the strong association with this disorder, with bilaterality of CHRPE considered strongly correlating with FAP [42, 44]. In certain circumstances, ocular screening is considered in individuals at risk for FAP, specifically those who have a first-degree relative with confirmed APC gene mutation but who have not themselves undergone genetic or confirmatory testing [44].

In addition to colorectal carcinoma, hepatoblastoma occurs among the malignancies seen in the FAP population. This malignancy is the most common liver malignancy seen in children and occurs most often in children under age three years old. While it is known to be associated with FAP, it is less commonly seen with this disorder [45]. Mutations in the APC gene affect the *Wnt/*β-catenin contributing to the origins of hepatoblastoma. Since this malignancy occurs most often at a notably young age, and a minority yet considerable portion of APC gene mutations seen in FAP are de novo, diagnosis of hepatoblastoma may be one of the earliest indicators of FAP in patients with a spontaneous FAP mutation [42]. Given the early onset of both hepatoblastoma and CHRPE in patients with FAP, these findings, when seen in conjunction, may strongly indicate concerns for FAP.

Figure 8: Congenital hypertrophy of retinal pigment epithelium (CHRPE).

Wernicke's Encephalopathy

Wernicke's encephalopathy is commonly associated with poor diet in the setting of alcoholic liver disease, although may be seen in other settings as well [46]. This condition presents with cranial nerve palsies, nystagmus, altered mental status, and gait disturbances. Wernicke's encephalopathy is caused by a deficiency of thiamine, which plays a crucial role in cellular metabolism specifically in the production and availability of ATP. Most typically, Wernicke's encephalopathy is associated with hepatic disorders due to underlying alcohol dependence which can result in alcoholic liver disease as well as other complications [46, 2]. In addition, thiamine is mainly stored in the liver, and thus end-stage chronic liver failure may cause depletion of thiamine and result in Wernicke's encephalopathy. This condition is notably underdiagnosed, with 80% of patients who experience Wernicke's encephalopathy not receiving a diagnosis as such. Unfortunately, unrecognized cases can end in permanent neurologic damage and even death. When this disorder is identified, patients are treated with thiamine. Many individuals are risk for thiamine deficiency are recommended increased thiamine intake, with thiamine fortification becoming increasingly common globally [46].

Conclusion

In conclusion, recognition of the relationship between ophthalmologic disease and hepatic disease has significant clinical implications. In many instances, systemic diseases including those with considerable hepatic manifestations may first be detected by ocular abnormalities. Examples include Septo-optic dysplasia, Gaucher disease, and galactosemia. In other instances, ophthalmologic findings can be used to clarify or confirm a diagnosis, such as in Wilson's disease, Alagille syndrome, Neiman-Pick, and Sandhoff disease. Patients may experience enormous benefit from their providers performing careful eye evaluation and understanding the clinical context of the presentation.

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