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Ophthalmological Findings in Metabolic Diseases

Metabolik Hastalıklarda Göz Bulguları

Oya KIREKER KÖYLÜ[1], Çiğdem Seher KASAPKARA[2]

[1] Department of Pediatric Metabolism, Ankara Bilkent City Hospital, Ankara, Türkiye
[2] Department of Pediatric Metabolism, Ankara Bilkent City Hospital, Ankara Yıldırım Beyazıt University, Ankara Türkiye

ABSTRACT

Inherited metabolic diseases are rare genetic disorders caused by synthesis disorders affecting protein, carbohydrate and lipid metabolisms, impaired enzyme activity, and deficiency of cofactors or transporters. More than 1000 inherited metabolic diseases have been reported. The prevalence of each disease is rare. However, the overall prevalence is not rare as expected. Inherited metabolic diseases can occur at any age, from prenatal to adulthood. The clinical features are mostly progressive when left untreated. Most diseases occur at young ages and often with more than one organ involvement. In Inherited metabolic diseases, eye involvement may be primary or secondary, and the findings may be local or systemic. The toxic effect of abnormal metabolites or accumulation of normal metabolites is usually responsible for the pathogenesis. Early recognition of treatable inherited metabolic diseases is important as it may change the treatment outcome of the patient. Ophthalmological findings may be in the form of cataract, corneal clouding, retinitis pigmentosa, cherry red spot and optic atrophy. Bilateral symmetrical involvement is expected. In this article, eye findings that can be seen in hereditary metabolic diseases will be discussed.

Key Words: Ophthalmological findings, Inherited metabolic disorders, Rare Diseases

ÖZ

Kalıtsal Metabolik Hastalıklar; protein, karbonhidrat ve lipid metabolizmalarını etkileyen sentez bozukluklarından, bozulmuş enzim aktivitesi, kofaktör veya taşıyıcı protein eksikliğinden kaynaklanan nadir görülen genetik bozukluklardır. 1000'den fazla hastalık bildirilmiştir. Metabolik hastalıklar her biri ayrı ayrı düşünüldüklerinde seyrek görüldükleri düşünülse de toplu olarak düşünüldüğünde önemli bir grup hastalığı oluşturmaktadır. Kalıtsal metabolik hastalıklar doğum öncesi dönemden yetişkinliğe kadar her yaşta ortaya çıkabilir. Klinik özellikler tedavi edilmediği taktirde çoğunlukla ilerleyicidir. Çoğu hastalık; genç yaşlarda ve sıklıkla birden fazla organ tutulumu ile ortaya çıkar. Kalıtsal metabolik hastalıklarda göz tutulumu primer veya sekonder olabileceği gibi bulgular lokal veya sistemik olabilir. Patogenezden genellikle anormal metabolitlerin toksik etkisi veya normal metabolitlerin birikimi sorumludur. Tedavi edilebilir kalıtsal metabolik hastalıkların erken tanınması, hastanın tedavi sonucunu değiştirebileceği için önemlidir. Oftalmolojik bulgular katarakt, korneal bulanıklık, retinitis pigmentoza, kiraz kırmızısı leke ve optik atrofi şeklinde olabilir. Bilateral simetrik tutulum beklenmektedir. Bu makalede kalıtsal metabolik hastalıklarda görülebilecek göz bulguları tartışılacaktır.

Anahtar Kelimeler: Göz bulguları, Kalıtsal metabolik hastalıklar, Nadir Hastalıklar

INTRODUCTION

The eye is the most specialized organ and enables us recognize the world around us. It has important physiological connections with the central nervous system (CNS), it gives symptoms in diseases affecting the CNS. Since the eye is a complex organ, one or more structural or functional components may affect vision. Several studies have shown that; Ocular manifestations occur in approximately one-third of inherited metabolic disorders. The occurrence of eye pathologies is not yet clear, but may be by direct toxic mechanisms of abnormal metabolic products or by the accumulation of normal metabolites. Eye involvement is not life-threatening, but may cause vision loss and affect the patient's quality of life. Eye pathologies are detected as an additional finding of hereditary metabolic

0000-0001-6822-1713 : KIREKER KÖYLÜ O
0000-0002-3569-276X : KASAPKARA ÇS

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Correspondence Address / Yazışma Adresi:
Oya KIREKER KÖYLÜ
Department of Pediatric Metabolism,
Ankara Bilkent City Hospital, Ankara, Türkiye
E-posta: oyam01@hotmail.com

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disease in the follow-up or the patient presents with primary eye findings and may indicate a hereditary metabolic disease. Symmetrical bilateral involvement is the rule in inherited metabolic diseases. Detailed clinical evaluation is essential to identify inherited metabolic disease. Congenital severe visual impairment is usually not noticed until about 2 months of age, when normal children can make eye contact. Severe visual impairment should be detected in the first weeks of life (1,2). Common eye findings that may occur in inherited metabolic diseases are as follows: corneal clouding, lens abnormalities, retinal degeneration, cherry red spot and optic atrophy.

CORNEAL CLOUDING

Anterior segment abnormalities of the eye can be easily detected on rapid eye examination using a slit lamp microscope. Ophthalmic phenotypes are corneal clouding or lens opacity. Corneal tissue consists of three components such as epithelium, stroma and Descemet's membrane. IMDs often show corneal opacities or clouding. Corneal transparency is dependent on collagen fibers and proteoglycans. Corneal opacities are common in lysosomal storage disorders such as X-linked Fabry disease because more than 70% of patients have corneal verticillata. Yellowish-gray deposits of glycosaminoglycan deposits in all layers of the cornea have been reported frequently in MPS I, IV and IV patients, and rarely in MPS II patients. This feature is also not detected in MPS III patients. A ring of copper can be seen in Descemet's membrane of the cornea in patients with Wilson's disease. In patients with cystinosis, cystine crystals in the cornea appear after 1 year of age. While renal complications predominate in the early forms of cystinosis, corneal cystine deposition will manifest in all patients with cystinosis. Inherited metabolic diseases affecting the cornea are numerous and severe. Lysosomal storage diseases are one of the most common inherited metabolic diseases that cause corneal clouding (3) (Table I).

Mucopolysaccharidoses (MPS) are a rare group of lysosomal storage diseases characterized by the accumulation of incompletely degraded glycosaminoglycans in many organs, including the eye. Ocular findings seen in MPS often result in visual impairment. Ocular complications are retinopathy, corneal opacity, and increased intraocular pressure. It is very difficult to detect corneal opacification due to mental problems, thickening with glaucoma and ocular hypertension in MPS patients. All patients with MPS types I, IV, and VI are affected by progressive corneal opacities. In MPS IS (Scheie's disease) and MPS II, corneal clouding is mild. It rarely requires corneal transplantation. Corneal clouding is not a prominent feature for MPS III (Sanfilippo syndrome). Progressive corneal opacification is seen in MPS VII (Sly syndrome). In MPS IV (Morquio's disease), keratan sulfate accumulates in the cornea. The accumulation of glycosaminoglycans in the corneal stroma causes a progressive increase in corneal thickness. In MPS VI and VII, the corneal epithelium is normal or minimally affected as in MPS I. Edema in the cornea is not a pathological feature. Corneal clouding is the result of storage in stromal keratocytes. Other ocular manifestations such as cataract, pigmentary retinopathy, glaucoma, and optic atrophy are also quite common in MPS In the past, the ocular pathology of many patients with MPS was inadequately treated. In recent years, treatments such as enzyme replacement therapy and bone marrow transplantation have provided a better quality of life for many MPS patients. These treatments do not completely remove ocular pathologies, but they are effective in reducing or stabilizing the symptoms (3).

Table I: Inherited Metabolic Diseases with Corneal Clouding

Lysosomal Storage Disorders
Mucopolysaccharidosis
Mucolipidosis
Mannosidosis
Farber's disease
Fucosidosis type III
Multiple sulfatase deficiency
Fabry disease
Cystinosis
Lipid metabolism disorders
Fish eye disease
Lecithin: cholesterol acyltransferase deficiency
Homozygous familial hypercholesterolemia
Disorders of amino acid metabolism
Alkaptonuria
Tyrosinemia type II
Metal transport disorder
Wilson's disease

Fabry disease also known as Anderson-Fabry disease is an X-linked lysosomal storage disease caused by insufficient activity of lysosomal α-galactosidase. Multiorgan involvement is seen. Estimated worldwide prevalence is 1:40,000 to 1:117,000. One of its local manifestations is the development of dystrophic changes in the structure of the cornea. Cornea, lens and conjunctival-retinal vessels are involved. In Fabry disease, there is a progressive accumulation of glycosphingolipids in the eye 'Cornea verticillata'. The prevalence of cornea verticillata is similar in different age groups. Cornea verticillata is seen in 80% of Fabry patients and is recognized by slit lamp examination. In early stages, fine horizantal lines are seen progressing to curving lines. Generally, vision is not affected. Differential diagnosis of Cornea verticillata includes the chronic use of medications like amiadorone and chloroquine. There are two types of cataracts (anterior and radial posterior subcapsular cataracts) described. These eye pathologies can be detected by slit lamp examination. Conjunctival and retinal vascular lesions, which are part of systemic vascular involvement, are also quite common. Irregularities of vessels (conjunctival and retinal vessels) occur by deposition of globotriaosylceramide (Gb3). This results in vascular tortuosity. Other ocular abnormalities rarely seen in Fabry disease are lid edema, chemosis, dry eye, papilledema and optic atrophy. Enzyme replacement therapy does not

change the ocular manifestations of Fabry disease (4).

Corneal involvement is also an early sign in other lysosomal storage diseases. Visual impairment and corneal clouding are evident in Mucolipidosis type IV. First, corneal clouding, then retinal degeneration and blindness may develop. Cytoplasmic membranous bodies are found in a variety of tissues. Patients are often mentally handicapped. In late-onset alpha-mannozidosis; hearing loss, corneal clouding, cataract and bone findings can be seen. The clinical findings of late onset forms of galactosialidosis are coarse face, mental retardation, hearing loss, growth retardation, joint stiffness, cardiac involvement, vertebral anomalies and seizures. In the second decade of life, loss of visual acuity, corneal clouding, bilateral cherry-red spots, dotted lens opacities, and color blindness are seen. In steroid sulfatase deficiency, corneal opacities, small punctate or filiform lesions are seen (5).

Cystinosis is a multisystem metabolic disease caused by mutations in the CTNS gene, which encodes the lysosomal carrier protein cystonin. Conjunctiva, cornea, iris, choroid and retinal pigment epithelium are affected due to the accumulation of cystine in lysosomes. Polychromatic corneal crystals extending from the periphery to the center are found in the anterior stroma. Photophobia is seen as a result of crystal deposition in the front camera. The first sign of the disease may be an ocular sign. Eye pathologies can be seen before nephropathy, eye examination is very important in patients with cystinosis. Corneal crystal accumulation can cause erosions. As a result of erosions of the corneal epithelium; eye watering, photophobia and blepharospasm may develop. In a severe form of the disease, cataracts, pigmentary retinopathy and blindness can occur. Cysteamine eye drops are used to reduce crystal deposits in the cornea. Corneal transplantation can be performed for visual rehabilitation (6).

Hypoalphalipoproteinemia such as Tangier disease, Lecithin cholesterol acyltransferase deficiency and apoprotein A-1 (Apo A-I) deficiency, is an inherited dyslipidemia characterized extremely low HDL-C values. Rare complications may include corneal opacities that typically do not affect vision. In patients with cyclomicronemia (hypertriglyceridemia), lipemia retinalis can be seen. Ocular findings are creamy discoloration of retinal vessels. Lipemia retinalis also does not affect the visual acuity. Familial hypercholesterolemia is an autosomal dominant disorder of lipid metabolism. Arcus cornea is an important sign and appears as single grayish ring parallel to the limbus. It is caused by lipid deposits in corneal stroma (7-10).

Tyrosinemia Type II, is an extremely rare autosomal recessive inherited metabolic disorder also called oculocutaneous tyrosinemia occurs due to deficiency of cytosolic tyrosine aminotransferase (TAT). Main manifestations of this enzyme deficiency are bilateral corneal erosions as well as palmar and plantar hyperkeratosis. Common complications are corneal opacity, glaucoma, corneal plana, nystagmus, visual impairment and amblyopia. Treatment consists of phenylalanine and tyrosine restricted diet. The target is to keep the tyrosine blood level at <500 micromol (11). Eye symptoms improve in a few weeks with treatment.

Alkaptonuria is a rare autosomal recessive metabolic disease caused by deficiency of homogentisate 1,2-dioxygenase (HGD) that results in harmful abnormal deposits in various tissues. Deficiency of HGD enzyme causes accumulation of homogentisic acid, tyrosine and phenylalanine. Oxidized pigment derivative bind collagen, causing their deposition in the connective tissue of the nose, sclera and earlobes. The ocular manifestations may occur as the renal and joint involvement. Eye pathologies occur in 70% of patients. Hyperpigmentation of the sclera can present and can be identified with gross examination without using any equipment. Wilson's disease is an autosomal recessive disease that causes copper to accumulate in the liver, kidneys, and nervous system. The characteristic ocular finding is Kayser-Fleischer ring typically starts without symptoms at the vertical poles of the cornea due to the deposition of copper in its deeper layers and progresses circumferentially. It may be visible to the naked eye as a golden-brown ring when it develops, but early stages can be seen by magnified examination with slit lamp examination. The ring decrease with treatment when serum copper levels become normal values. Similar rings can be seen in other causes of liver failure, such as carotenemia and multiple myeloma, in asymptomatic affected individuals. Therefore, it is certainly not pathognomonic for Wilson's disease. Rings can heal after copper chelation therapy (12).

LENS ABNORMALITIES

Cataract

Congenital cataracts are rare but the most important reason of treatable childhood blindness. Cataract is the opacity within the lens. Cataract and lens dislocation are frequently seen in inherited metabolic diseases. If lens opacities are not diagnosed or treated at birth, they can cause blindness or amblyopia (13). When the patient is 3 months old, bilateral cataract causes irreversible nystagmus and amblyopia. For this reason, cataracts must be surgically removed within the first few weeks of life. Some inherited metabolic diseases also manifest themselves with cataracts (Table II). Unilateral cataracts are often associated with eye malformations whereas bilateral cataracts are more often associated with genetic metabolic disorders (14,15). Due to the lack of systemic associations in unilateral cataract, it is generally agreed that these children do not require further work up. Systemic work-up is necessary in children with bilateral cataracts (16,17).

Classic galactosemia is a disorder of the galactose metabolism and is inherited as autosomal recessive manner. It is caused by deficiency of GALT enzyme. Galactose-1-phosphate uridyltransferase (GALT), galactose1-phosphate epimerase and galactokinase are the three enzymes involved in galactose metabolism. In the early stage, "oil droplet" cataracts are seen,

Table II: Inherited metabolic diseases with cataract
Galactosemia
Zellweger syndrome
Rhizomelic chondrodysplasia punctata
Lowe's syndrome
Sorbitol dehydrogenase deficiency
Aldose reductase deficiency
Fabry disease
Neuronal ceroid lipofuscinosis (juvenile form)
Oligosaccharidoses:α-mannosidosis; sialidosis
Lysinuric protein intolerance
Ornithine aminotransferase deficiency
Sjogren-Larsson syndrome
Neutral lipid storage disorder
Cerebrotendinous xanthomatosis
Smith – Lemli – Opitz syndrome
Conradi-Hunermann syndrome
Mevalonate kinase deficiency
Sengers syndrome
Methylglutaconic aciduria
Mitochondrial DNA mutations
Menkes disease
Wilson's disease

which are not true cataracts but produce refractive changes in the lens. The lesion appears as a floating oil droplet in the center of the lens (13). Galactitol, a metabolite of galactose, accumulates in the lens. Galactitol is impermeable and causes deterioration of the lenticular structure. Hepatic failure, jaundice and tubulopathy are seen in GALT deficiency. Diagnosis is made by measurement of GALT enzyme activity in erythrocytes and molecular analysis for confirmation. Epimerase deficiency is caused by GALE gene defects and three forms have been defined. The polyol pathway consists of two enzymes; aldose reductase and sorbitol dehydrogenase. Aldose reductase reduces hexose sugars such as glucose and galactose to sorbitol and galactitol. As a result of polyol accumulation; lens swelling, increased membrane permeability, electrolyte abnormalities and increased intracellular fluid are seen. This causes cataracts. In sorbitol dehydrogenase deficiency, cataract occurs as the only finding at birth. Determination of galactose metabolizing enzymes, sorbitol dehydrogenase in lens, may help in determining the mechanism of formation of cataracts. Cataract may also develop in glucose-6-phosphate dehydrogenase deficiency (G6PD), which is noted with hemolytic anemia. Glucose-6-phosphate dehydrogenase has an essential role in the defense against cellular injury. The most common manifestations of G6PD deficiency is jaundice and hemolysis. Cataract is less known finding described with G6PD deficiency. Oxidative stress is responsible in the pathogenesis of cataract (18,19).

Among the known membranes, the membrane with the highest cholesterol content is the lens membrane. It is of great importance that cholesterol metabolism is normal in the continuity of the lens. It is manifested by disorders of cholesterol biosynthesis and a wide and variable distribution of congenital anomalies. Cataracts can be seen in very severe forms in the early period. In mild forms, cataracts may not develop. In Cerebrotendinous xanthomatous; xanthomas are associated with progressive neurological ataxia syndrome, cognitive impairment, pyramidal manifestations, epilepsy, peripheral neuropathy and eye pathologies such as bilateral, irregular, corticonuclear, anterior polar or posterior capsular cataracts that occur in the first decade. It may be related to the opacities of the crystalline lens. Cataracts can also be seen in patients with Sjögren-Larsson syndrome and neutral lipid storage disorder characterized by ataxia, myopathy, hepatomegaly and ichthyosis. Vacuolated lymphocytes are a common finding in peripheral smear (7,20).

Zelweger spectrum disorders are heterogenous group of autosomal recessive disorders characterized by a defect in peroxisome formation. Mutations in *PEX* genes cause a deficiency of functional peroxisomes. Ocular abnormalities like retinopathy, cataracts and glaucoma often leading to blindness could be seen (21). Measurement of plasma very long chain fatty acids is helpful in diagnosis but molecular genetic analysis should be done for accurate diagnosis (22). It is important to initiate proper supportive therapy to improve quality of life.

Cataracts can also be seen in other aminoacidopathies such as ornithine aminotransferase (OAT) deficiency (gyrate atrophy of the choroid and retina) and lysinuric protein intolerance. In Lowe's (oculo-cerebro-renal) syndrome, cataract is a prominent finding in the disease. Severe neurological involvement such as muscle hypotonia, areflexia, renal involvement (Fanconi syndrome) and mental retardation are other clinical findings of Lowe's syndrome (23,24).

Lens Dislocation

Lens dislocation is a common and characteristic feature of both Marfan syndrome and homocystinuria. Marfan syndrome is a rare inherited disorder of the connective tissue with autosomal dominant mode of inheritance. Microfiber abnormalities are seen in the lens capsule due to changes in microfibers caused by mutations of the fibrillin-1 (*FBN1*) gene in Marfan syndrome. The clinical findings are are tall stature with a large arm span, kyphosis, congenital lens dislocation and cardiac manifestations. In homocystinuria, lens subluxation is most common downward, whereas in Marfan syndrome, the lens usually subluxes upwards. However, it can be in any direction in both diseases (25,26) (Table III). Most patients with Isolated sulfite oxidase deficiency develop microcephaly, feeding difficulties and dislocated ocular lenses. In patients with homocystinuria, subluxation of the ocular lens occurs in more than 90% of patients and is very characteristic. As it can be seen before 3 years of age, it usually presents until the first 10 years of age. Worsening myopia, astigmatism, and glaucoma may also occur. Cataracts may occur in the lens. Optic atrophy may develop following retinal detachment and central retinal artery occlusion. Hypermethioninemia is an important finding. Diagnosis is made by measuring cystathionine β-synthetase enzyme activity in fibroblast culture, lymphoblasts and mutation analysis. In patients diagnosed with newborn screening, diet

Table III: Inherited metabolic diseases with Lens Dislocation
Marfan Syndrome
Homocystinuria
Sulfite oxidase deficiency
Molybdenum Cofactor deficiency

therapy (low in methionine) and pyridoxine should be started. Thus, it is possible to prevent lens dislocation in early detected patients (26).

RETINAL DEGENERATION

The retina is a target for defects of oxidative phosphorylation. Retinal involvement occurs as retinitis pigmentosa or optic atrophy. Diseases characterized by the presence of retinal pigmentation as a prominent feature of retinal degeneration are overviewed. Retinitis pigmentosa and optic neuropathy are very frequent in mitochondrial disorders.

Retinitis Pigmentosa is a group of inherited diseases in which progressive loss of photoreceptor and pigment epithelial function occurs. The genetic defect is expressed in the rods, but in most affected people the cones finally degenerate resulting in loss of central vision. Bilateral peripheral vision loss, rod dysfunction and progressive loss of photoreceptor function are diagnostic criteria. RP usually begins in early childhood or infancy. The earliest ophthalmoscopic findings are a thread-like appearance of retinal arteries and a weak retinal reflex. Anomalies in RP can be detected by electroretinogram before they have fundoscopic findings. It can be divided in two groups as primary and secondary RP. Gyrate atrophy of the choroid and retina caused by OAT deficiency can be given as an example to the first group. RP is frequently associated with some genetic disorders impairing mitochondrial OXPHOS. Two of them are neurogenic muscle weakness with retinitis pigmentosa (NARP) and sporadic Kearns-Sayre syndrome (KSS). Retinitis pigmentosa can also be seen in lipid metabolism disorders such as abetalipoprotenemia and lysosomal storage disorders as shown in Table IV.

Gyrate atrophy of the choroid and retina is a rare metabolic disease caused by deficiency of the enzyme ornithine aminotransferase (OAT) which is pyridoxal 5-phosphate dependent and located in mitochondrial matrix. Elevated concentration of ornithine occurs in body leads to characteristic ocular abnormalities. Patients usually present to the ophthalmologist with night blindness or myopia in late childhood or adolescence. Posterior subcapsular cataract develops in the twenties. In the third decade, most of the fundus is involved and pigmentation increases in the macular region. The optic disc is pink. Visual acuity and visual fields gradually decrease. In OAT deficiency, ornithine level increases 10-15 fold in all body fluids including aqueous humor along with a small reduction in glutamine, lysine and creatine and causes lesions in photoreceptors. Treatment is not curative and depends on life long dietary modifications (arginine restriction and lysine supplementation) and vitamin B6 administration which aims to increase plasma pyridoxal 5-phosphate level (24-28). Inherited metabolic diseases causing secondary retinitis pigmentosa are described in Table IV.

Table IV: Inherited metabolic diseases with retinitis pigmentosa
Lysosomal storage diseases
Lipid metabolism disorders
Mitochondrial diseases
Peroxisomal disorders

Neuronal Ceroid lipofuscinoses (NCLs) are among gray matter neurodegenerative disorders. NCLs are a group of progressive encephalopathies characterized by neural and extraneural accumulation of autofluorescent ceroid and lipofuscin material. NCL types that cause RP are divided according to clinical and genetic variants (29,30).

1. ***Palmitoyl protein thioesterase-1 related NCL (CLN1):*** Common presenting findings included motor delay or regression, abnormal movements, visual impairment, microcephaly and myoclonic epilepsy are seen.
2. ***Tripeptidyl-peptidase-1 related NCL (CLN2):*** Clinical findings start between the ages of 2-4; regression in mental abilities, ataxia, convulsions, optic atrophy on fundus examination and pathological electroretinogram and visual evoked potentials (VEP) are seen.
3. ***Juvenile neuronal ceroid lipofuscinosis (CLN3):*** The majority of the patients suffer from neurological degeneration in the first decade and rapid visual decline after 5 years of age due to retinal degeneration. It limits the life expectancy to 20 years of age.

Retinitis pigmentosa can also be seen in different lipid metabolism disorders such as abetalipoproteinemia, malabsorption of fat-soluble vitamins, especially vitamins A and E. The most common clinical symptoms are diarrhea and growth retardation. Peripheral neuropathy, spinocerebellar ataxia, and muscle weakness are also seen. Retinal dystrophy usually occurs in late childhood. Fundus examination may be normal in the early period, then there may be peripheral pigmentary retinopathy. Retinal and neurological complications can be prevented by early supplementation of vitamin E (31,32).

CHERRY RED SPOT

A cherry red spot is formed due to ganglioside deposition in retinal ganglion cells. Sialidosis is an autosomal recessive disorder resulting from mutations in NEU1 gene. There are two forms defined. Sialidosis I is often referred as myoclonus-cherry red spot syndrome presenting in second decade of life with visual decline. Type II is more severe acute fulminant

form. Galactosialidosis is also autosomal recessive inherited metabolic disease caused by mutations in *CTSA* gene leading to combined deficiency of neurominidase and beta-galactosidase. Common clinical features are coarse face, skeletal abnormalities, myoclonus, cherry red spot in macula and seizures. Cherry red spot is also a common feature of other lysosomal storage disorders such as Tay-Sachs disease, Sandhoff disease and Niemann Pick disease. GM1 gangliosidosis is a lysosomal storage disorder caused by low activites of beta- galactosidase enzyme and pathogenic mutations in *GLB1* gene. The clinical features are psychomotor regression, visceromegaly, extensive Mongolian spots on the trunk, coarce facial appearence, retinal cherry red spot and skeletal abnormalities. GM2 gangliosidosis include Tay-Sachs disease, Sandhoff disease and GM2 activator protein deficiency. Sandhoff disease is an autosomal recessive lysosomal disorder resulting in GM2 gangliosidoside storage due to deficiency of Beta-hexosaminidase B (*HEX-B*). There are three clinical phenotypes exist. Most common subtype is infantile onset one which is characterized by axial hypotonia, startle response, macrocephaly, seizures and macular cherry red spots and finally died before 5 years of age. Farber disease is an ultra-rare lysosomal disorder caused by acid ceramidase deficiency encoded by *ASAH1* gene. Cardinal clinical findings include subcutaneous nodules, joint contractures, and hoarce voice. Ophtalmic symptoms such as formation of cherry red spot, storage pathology in retinal ganglion cells, corneal opacities and nystagmus may be present in patients with Farber disease. Pigment retinopathies are one of the ocular findings seen in many lysosomal storage diseases. The absence of ganglion cells in the fovea causes a red stain surrounded by white cells filled with storage material. As the ganglion cells die, the cherry-red spot disappears, optic atrophy becomes evident. In the differential diagnosis, mainly lysosomal storage diseases should be considered. It can be detected early in GM2 gangliosidosis and GM1 gangliosidosis. Electroretinogram is normal, but VEP is abnormal. The cortical response usually disappears from the first months of life (33,34). In Niemann-Pick disease type A, corneal opacification and dislocation of the anterior lens capsule are seen. In sialidosis (mucolipicosis type I), cherry- red spot is seen. Irregular pale cherry red spot is also seen in Farber's disease, Gaucher's disease type II and GM2 activator protein deficiency (5,35) (Table V). Retinal degeneration can also be seen in intracellular cobalamin metabolism defects and congenital glycosylation defects.

Table V: Inherited metabolic diseases with cherry-red spot

Tay–Sachs disease
Sandhoff disease
Niemann–Pick disease type A
Gaucher disease type II
Farber's disease
Sialidosis types I, II
Galactosialidosis
GM1 gangliosidosis
GM2-activator protein deficiency

OPTIC ATROPHY

Optic atrophy is a manifestation of the degeneration of ganglion cell axons forming the optic nerve or the supporting microvascular tissue surrounding the optic nerve. Decreased visual acuity, visual field defects and/or color vision disturbances are seen. The early stage of optic atrophy before clinical signs appear is called optic neuropathy. It is a general term for optic nerve dysfunction. Progression of optic atrophy can be stopped by treating an underlying cause. However, there is no effective treatment. Genetic defects are responsible for a significant portion of optic atrophy. The lesion may be the only clinical feature (primary) or it may be associated with various symptoms (secondary) (36).

Optic atrophy is often the only clinical feature of the disease. Examples of primary causes are Leber's hereditary optic neuropathy (LHON) and Costeff syndrome (37).

Leber hereditary optic neuropathy (LHON) is an inherited metabolic disease of mitochondrial inheritance. The pathogenesis involves a primary point mtDNA mutation resulting in failure of the oxidative phosphorylation pathway. Vision loss that mostly affects young men. It is typical of mitochondrial optic neuropathies. Rapid, painless loss of central vision in one eye is characteristic. It usually starts with discoloration in one eye, and then a similar involvement is seen in the other eye and visual acuity stabilizes within a few months. Visual field defect in the form of centrocecal absolute scotoma is seen (37). The symptomatic phase of LHON is characterized by an acute or subacute bilateral painless central vision loss associated with swelling of the nerve fiber around the disc and telangiectatic microangiopathy in peripapillary region without leakage on fluorescein angiography. The optic disc appears hyperemic, sometimes with peripapillary hemorrhages, and axonal loss quickly leads to transient atrophy of the optic disc. Over time, the optic disc becomes pale. Optic atrophy occurs with permanent severe central vision loss but with relative preservation of the pupillary light reflex. However, over time, visual acuity improved spontaneously. Visual function may suddenly improve with the contraction of the scotoma or the reappearance of small islets of vision (fenestration) in it. In long-term LHON, dimpling of the optic disc can often be a manifestation of the chronic stage of the pathological process. LHON typically results from homoplasmic mtDNA mutations with wide variability in phenotypic penetration (38). The diagnosis of LHON can be made based on patient and family history, as well as neuroophthalmologic examination and mDNA genetic analysis. Confirmation of the diagnosis is very important because of the clinical course, prognosis and hereditary pattern of the disease. Idebenone is a synthetic water-soluble analog of co-enzyme Q10, the approved therapy for LHON. Approved treatment in LHON is limited, preclinical studies in gene therapy will be done (39).

Table VI: Inherited metabolic diseases with optic atrophy
Mitochondrial diseases
Peroxisomal diseases
Lysosomal storage diseases
Other metabolic disorders
Homocystinuria
Cobalamin C/D disorders
Propionic acidemia
Mevalonic aciduria
Smith – Lemli – Opitz syndrome
Alexander's disease
Canavan's disease
Menkes
Pelizaeus-Merzbacher disease

Costeff optic atrophy syndrome (OPA 3), is a disease consisting of early-onset bilateral optic atrophy and late-onset spasticity, extrapyramidal dysfunction, and cognitive problems.

Secondary optic atrophies are commonly caused by mitochondrial, peroxisomal, lysosomal and other metabolic diseases (Table VI) (40-44). Due to the crucial involvement of Krebs cycle in the maintenance and survival of retinal ganglion cells, patients with mitochondrial disease are prone to have optic atrophies.

Optic atrophies are described also in a variety of inherited metabolic disorders and may not be a permanent finding. Biotinidase deficiency, Menkes disease, homocystinuria, inherited disorders of cobolamin metabolism, Smith- Lemli-Opitz syndrome, congenital glycosylation defects and organic acidemias are examples of diseases that cause secondary optic atrophy.

CONCLUSION

Ocular symptoms often occurs in inherited metabolic diseases. Accurate examination of the eye with the aid of an ophthalmoscope and slit lamp can detect pathognomonic abnormalities such as corneal clouding, lens abnormalities, retinal degeneration, cherry red spot, cataract and optic atrophy. Ophthalmological evaluation are often non-invasive and provides important clues in the diagnosis of many inherited metabolic diseases. Inherited metabolic diseases should always be suspected when more common etiologies have been ruled out. Early management of ocular symptoms can improve the patient's quality of life.

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