

Narrative Review:

The Ophthalmological Manifestations of Various Inborn Errors of Metabolism: A Narrative Review



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Citation Medghalchi A, Hassanzadeh Rad A, Dalili S. The Ophthalmological Manifestations of Various Inborn Errors of Metabolism: A Narrative Review. Journal of Pediatrics Review. 2021; 9(2):137-144. <http://dx.doi.org/10.32598/jpr.9.2.584.1>

doi <http://dx.doi.org/10.32598/jpr.9.2.584.1>



Article info:

Received: 17 July 2020

First Revision: 25 July 2020

Accepted: 22 October 2020

Published: 01 April 2021

Keywords:

Inherited Metabolic Disorder (IMD), Ophthalmology, Eye

ABSTRACT

Context: Inborn errors of metabolism or Inherited Metabolic Disorders (IMD) are a class of genetic disorders that occur because of single-gene defects.

Evidence Acquisition: In this narrative review article, the authors searched Institute for Scientific Information (ISI), Web of Science, PubMed, and Google Scholar for the relevant evidence.

Results: The ocular manifestations of IMDs can be distinguished in different diseases such as Albinism, Cystinosis, Homocystinuria, and Sulfite oxidize deficiency, Mannosidosis, Fucosidosis, Sialidosis, etc.

Conclusions: Due to the direct toxic mechanisms of abnormal metabolites on eyes and regarding the effect of eye monitoring on the follow-up, management, and treatment, a detailed ophthalmological assessment is essential.

1. Context

Inborn errors of metabolism or Inherited Metabolic Disorders (IMD) are a class of genetic disorders that occur because of single-gene defects (1). It can be distinguished not only in neonates and infants but also in adults (2, 3). The diagnosis of IMD is challenging for physicians. Significant changes in the diagnosis, classification, and treatment of IMDs were improved by medical technologies and higher knowledge regarding the human genome.

These changes help the physician to recognize and treat patients earlier. There exist various recognized IMDs; a number of them are reported in Iran as biotinidase deficiency, methylmalonic acidemia, and non-ketotic hyperglycinemia (4-7). Early diagnosis, thorough laboratory assessments, and reference to tertiary care centers if needed are essential for these patients.

IMDs may induce small molecule diseases by affecting protein, carbohydrate, lipid, and nucleic acid. It can also be an organelle disease and impact lysosomes, mitochondria, peroxisomes, and cytoplasm. Besides, IMDs

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present diverse complications on the eyes, including the ocular abnormalities of conjunctiva, cornea, lens, retina, optic nerve, ocular motility or symmetrical bilateral involvement, as well as severe visual acuity in approximately 2-meter counting finger.

Despite extensive knowledge about the metabolic, biochemical, and molecular features of various IMDs, their exact pathogenesis requires further evaluation. Furthermore, assessing the effects of mechanisms contributing to systemic metabolic diseases to ocular defects needs to be clarified.

In this narrative review article, the authors searched Institute for Scientific Information (ISI), Web of Science, PubMed, and Google Scholar for the relevant evidence. We found several recent articles related to the effects of IMDs on the eyes. Authors collected and reported the overall ophthalmological problems consequent to the endocrinologists' needs regarding this issue in conferences. Besides, this article summarized the effects of

IMDs of amino acids, carbohydrate, lipid, glycoprotein, lysosomes, lipoprotein and lipid, and miscellaneous diseases, such as Wilson and Menkes diseases on eyes. A previous study reported a detailed article consisting of the pathophysiology and physiology of the disease and their influence on the eyes (8).

2. Results

Table 1 presents the classification of metabolic diseases affecting the eyes; the ocular manifestations of IMDs can be distinguished in different diseases.

Albinism: It is an inherited disorder of melanin synthesis. It has two types; the first type simultaneously affects the skin and eye (oculocutaneous), and the second type only involves the eye (ocular). The ophthalmic manifestations of both types of albinism are refractive errors, reduced visual acuity, Iris transillumination defects due to decreased iris pigmentation, foveal hypo-

Table 1. Classification of metabolic diseases affecting eyes

Conditions	Diseases
The conditions of amino acid metabolism	Albinism
	Cystinosis
	Homocystinuria
	Sulfite oxidize deficiency
	Hyperornithinemia (Gyrate atrophy)
	Tyrosinemia type II
	Hyperlysinemia
The conditions of carbohydrate metabolism	Galactosemia
The conditions of lipid metabolism	Niemann-pick disease
	Fabry's disease
	Gaucher disease
	Metachromatic leukodystrophy
	Gangliosidosis
The conditions of glycoprotein degradation	Mannosidosis
	Fucosidosis
	Sialidosis
Lysosomal storage disease	MPS
Lipoprotein and lipid disorders	Familial Hypercholesterolemia Cerebrotendinous xanthomatosis
Miscellaneous	Wilson's disease
	Menkes disease



Figure 1. The conditions induced by amino acid metabolism on eyes

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plasia, nystagmus, strabismus, albino fundus, and abnormal nerve fiber crossing (9).

Cystinosis: It is a metabolic disease that causes the accumulation of cystine in the cells. Its pathognomonic ophthalmic finding is the deposition of iridescent crystal in the peripheral cornea. The other ocular manifestations of cystinosis are the accumulation of crystals in the uvea, iris, ciliary body, and pigmentary retinopathy in the eye (10).

Homocystinuria: It occurs in the absence of cystathionine b-synthetase (the enzyme that converts homocysteine to cystathionine). The main ocular manifestation of homocystinuria is ectopia lentis. Lens subluxation is usually inferiorly; however, the luxation varies. The other ophthalmic manifestations are progressive myo-

pia, increased intra ocular pressure, retinal detachment, and optic atrophy (11).

Hyperornithinemia (Gyrate Atrophy): It is autosomal recessive dystrophy due to the deficiency of the activity of the mitochondrial matrix enzyme, ornithine aminotransferase, and the elevation of ornithine in plasma. The main ocular finding is hyperpigmented fundi that separates with the islands of loss of retinal pigment epithelium and chorioretinal atrophy. The other eye features are myopia, night blindness, and cataract (12).

Figure 1 shows the conditions concerning amino acid metabolism in eyes.

Classic Galactosemia: It is the deficit in the activity of galactose-1-phosphate uridyl transferase. A cataract may



Figure 2. The condition induced by carbohydrate metabolism on eyes

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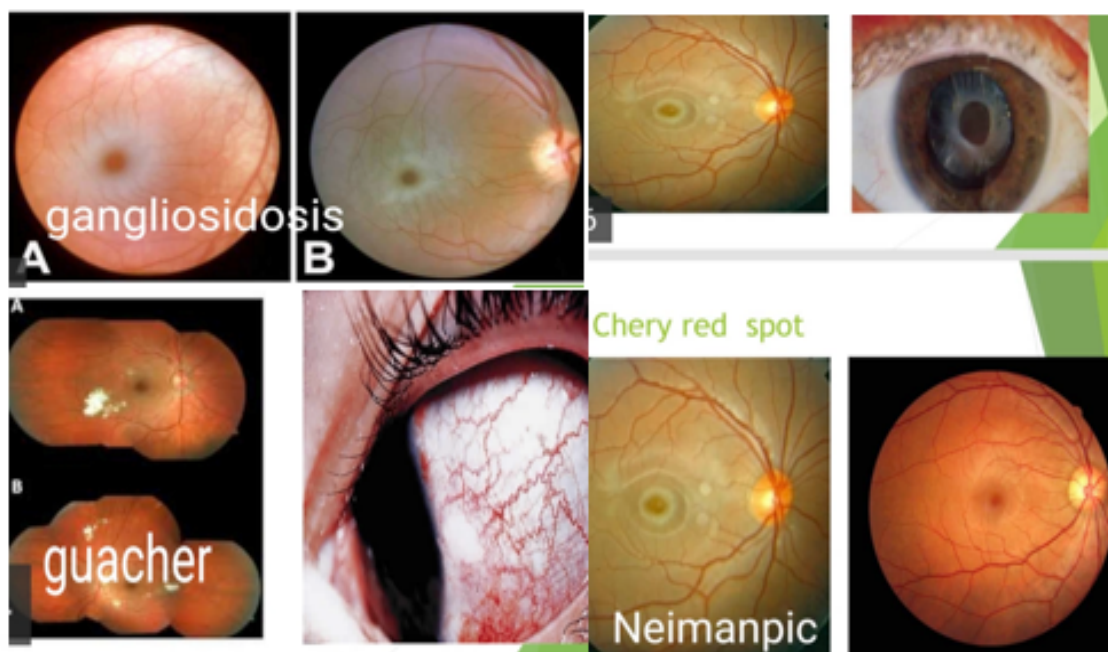


Figure 3. The disorders of lipid metabolism on eyes

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occur as a result of the accumulation of galactitol, i.e. the end metabolite of galactose in the nucleus and deep cortex of the lens. It induces an oil drop appearance on retroillumination (13). Figure 2 shows the disorder induced by carbohydrate metabolism on the eyes.

Niemann-Pick: It is a rare genetic disease generated due to sphingomyelinase isoenzymes that affect the body's ability to metabolize cellular cholesterol and lipids. There are 3 types of Niemann-Pick disease, including A, B, and C (14). There exist various eye involvement in Niemann-Pick disease.

Niemann-pick disease types A: It causes a cherry-red spot in the macula in 50% of infants. A brownish discoloration of the anterior lens capsule is another manifestation of type A.

Niemann-Pick Disease Type B: It is the mildest form of the disease. It causes a cherry-red spot in the macula, i.e. diagnostic.

Niemann-Pick Disease Type C: It has a vertical ophthalmoplegia and optic atrophy. There is no cherry-red spot present in this type (15).

Fabry disease: It is a rare inherited disease that prevents the body from making alpha-galactosidase A. The accumulation of ceramide triheoside was conducted on various tissues, such as blood vessels in the kidney, skin, gastrointestinal tract, central nervous system, heart, and eye. The relevant ophthalmic manifestations include increased vessel tortuosity and aneurysms in the conjunctiva, verticillata in the cornea, increased tortu-



Figure 4. The disorders of glycoprotein degradation on eyes

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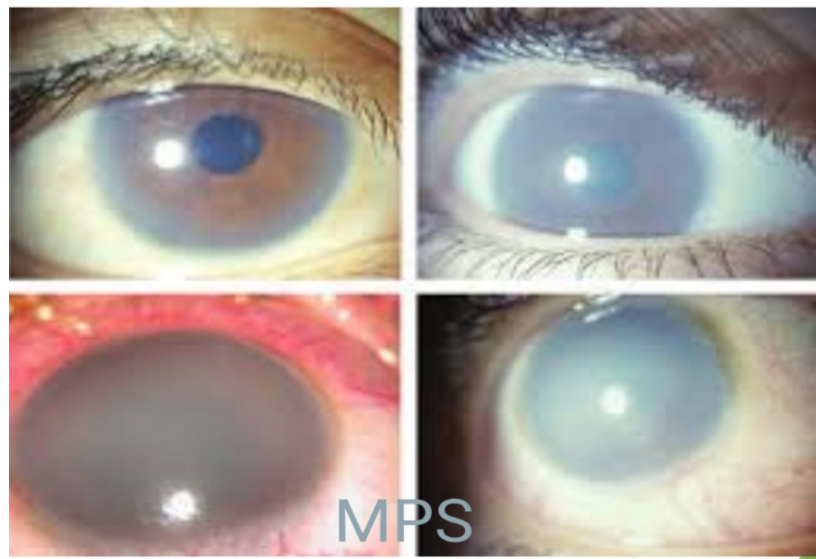


Figure 5. The effect of lysosomal storage disease on eyes

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osity of vessels in the retina, and faint spoke-like lines opacity at the posterior lens capsule in the lens (16).

Gaucher disease: It is the result of a buildup of certain fatty substances in specific organs, particularly the spleen and liver. It has 3 types; the ocular feature of Gaucher disease type 1 includes brownish pinguecula-like masses, containing Gaucher cells. In the retina, Gaucher cells can be observed as well. Gaucher disease, type 2 is the acute neuropathic infantile form that causes persistent retroflexion of the head and signs of pseudobulbar palsy. The classic Gaucher triad consists of Trismus, Strabismus, and Opisthotonus. Gaucher disease, type 3 has manifests features, such as ocular apraxia and corneal opacification (17).

Metachromatic Leukodystrophy (MLD): Multiple Sulfatase Deficiency (MSD) is a rare form of late-infantile MLD. Its ophthalmologic features consist of skew deviation, optic atrophy, retinal degeneration, and cherry-red spot (18).

Gangliosidosis: It is caused by the accumulation of gangliosides and contains different types of lipid storage disorders. The cherry-red spot is the eye manifestation of it (19). Figure 3 shows the disorders induced by lipid metabolism on the eyes.

Ophthalmologic manifestations of type I (infantile) mannosidosis is lens opacity in the posterior cortex. Type II (juvenile) mannosidosis induces Punctate opacity throughout the lens. The strabismus, pallor, and blurring of the optic disc and retinal degeneration are other manifestations of mannosidosis (20).

Fucosidosis is a lysosomal storage disease caused by defective alpha-L-fucosidase with the accumulation of fucose in the tissues. Its ocular features include vascular tortuosities, tortuous conjunctival vessels with microaneurysms, and dilated and tortuous retinal veins (21). Figure 4 shows the disorders of glycoprotein degradation.



Figure 6. The effects of miscellaneous disorders on eyes

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Lysosomal storage disease: Mucopolysaccharidosis (MPS) is a group of inherited lysosomal storage disorders. Their ocular manifestations are progressive corneal clouding, retinal pigmentary degeneration, diminished or extinguished electroretinogram, optic nerve head swelling, optic atrophy, and glaucoma (22). Figure 5 shows the effect of lysosomal storage disease on the eyes.

Wilson's disease: It is an inherited disorder in which excess copper builds up in the liver, kidney, and basal ganglia of the brain. It induces the Kayser-Fleischer ring in the cornea and sunflower cataract. Kayser-Fleischer ring is determined by the band of golden to greenish-yellow, bronze, or brownish hue in the Descemet membrane of the peripheral of the cornea. Sunflower cataract occurs in only 15% to 20% of the affected individuals; it is determined by fine deposits beneath the anterior and posterior lens capsule, forming a disc-like opacity axially. The opacities do not interfere with vision (23).

Menkes disease: It is an X-linked recessive disorder of copper metabolism. The ocular manifestations of Menkes disease are hypopigmented fundus, a decrease in the nerve fibers of the optic nerve, an increase in the glial elements, and the attenuation or tortuosity of the retinal arterioles (24). Figure 6 shows the effect of miscellaneous disorders on the eyes.

3. Conclusion

Metabolic diseases are rare disorders, i.e. difficult to be diagnosed. They are usually difficult to be diagnosed based on the clinical findings, laboratory results, and physical examination. Besides, there is a shortage regarding the reports of numerous metabolic disorders in the worldwide genetic banks. Commonly, other organs should be assessed to accelerate the diagnosis. The eye is among the most significant organs, i.e. the mirror of the brain. In these disorders, ophthalmologists can help endocrinologists by thorough assessments of layers, including the sclera, cornea, pupil, and so on. Sometimes, metabolic diseases are asymptomatic; accordingly, there is no specific symptom or sign for the detection of those, leading clinicians to compile all assessments and examinations to reach a decision. Therefore, due to the direct toxic mechanisms of abnormal metabolites on eyes and regarding the effect of eye monitoring on the follow-up, management, and treatment of IMEs, a detailed ophthalmological assessment is essential.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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