대한 유전성 대사 질환 : 2022;22(2):37~45

종 설

유전성대사질환에서 눈이상

서울대학교병원 안과

정 재 호

Inherited Metabolic Disorders Involving the Eye

Jae Ho Jung, MD

Department of Ophthalmology, Seoul National University Hospital

Inherited metabolic disorders (IMD) are a large group of rare disorders affecting normal biochemical pathways. The ophthalmic involvement can be very varied affecting any part of the eye, including abnormalities of cornea, lens dislocation and cataracts, retina and the optic nerve, and extraocular muscles. Eye disorders can be initial symptoms of some IMD and can be clue for diagnosis of IMD. However, eye disorders can evolve later in the natural history of an already diagnosed metabolic disorder. Awareness of IMDs is important to facilitate early diagnosis and in some cases instigate early treatment if a patient presents with eye involvement suggestive of a metabolic disorder. Ophthalmological interventions are also an important component of the multisystem holistic approach to treating patients with metabolic disorders.

Key words: Inherited Metabolic Disorders, Cornea opacity, Cataract, Retina dystrophy, Optic atrophy, Strabismus

Many inherited metabolic disorders (IMD) can have ophthalmic manifestations, including disorders of any part of the eye. Ophthalmic manifestations in IMD can be from cerebral visual cortex dysfunction in many IMD with progressive central nervous system degeneration, to optic neuropathy, retinopathy, lens opacification and cataracts, corneal clouding and various other keratopathies, and abnormalities of eye movements[1,2]. In some of IMD patients, eye involvement can be the primary presenting feature of an IMD that can lead to a diagnosis, for example, the identification of neonatal cataracts can be the first sign of disorders of galactose metabolism, while an incidental finding of cornea verticallata (vortex keratopathy) at a routine optician check can lead to the diagnosis of the lysosomal storage disorder (LSD).

Many IMD have ophthalmic involvement as an expected complication or sequela, and these patients will be referred to ophthalmology department to facilitate appropriate monitoring and treatment, and in this situation, it is important that knowledge of the natural history and expected evolution of the ophthalmological component of the IMD guides the clinical surveillance.

Corresponding: Jae Ho Jung, MD
Department of Ophthalmology, Seoul National University Hospital, 101, Daehak-ro Jongno-gu, Seoul, South Korea, 03080
Tel: +82-2-2072-1765, Fax: +82-2-747-5130
E-mail: jaeho.jung@snu.ac.kr

IMDs and eye movement disorders

1. Oculogyric crisis

Neonatal or early-onset oculogyric crisis may be due to a defect in neurotransmitter metabolism, and will usually be seen as part of a severe neurological

phenotype with hypertonia and/or seizures; these can occur in disorders of vitamin B6 metabolism that are treatable with oral vitamin B6 supplementation. Diagnosis usually requires cerebrospinal fluid analysis of neurotransmitters together with molecular genetic testing. Treatment will depend on the specific diagnosis, and may include neurotransmitter replacement or specific blockade therapies.

2. Strabismus and ophthalmoplegia

The differential diagnosis of new onset strabismus in early childhood is broad including simple refractive errors, space occupying lesions, but also including IMD. Strabismus is a feature of the commonest form of congenital disorder of glycosylation (CDG), phosphomannomutase 2 (PMM2-CDG). Ocular involvement in this multisystem disorder can also include nystagmus with or without visual impairment, and other subtypes of CDG also have eye involvement. Extraocular manifestations are expected including dysmorphic features, protein-losing enteropathy, pericardial effusions[3]. Early-onset mitochondrial disorders including those presenting with Leigh and Leigh-like syndrome can present with new-onset strabismus together with other loss of previously acquired skills often after a minor febrile illness; imaging studies together with biochemical testing are the first steps in the diagnostic workup. Mitochondrial disorders can also present later in life with primary ocular motor defects, including progressive external ophthalmoplegia as either an isolated feature, or as part of a multisystem mitochondrial defect such as chronic progressive external ophthalmoplegia (CPEO) (Fig. 1). Some LSDs have specific eye movement abnormalities. Gaucher disease can be associated with a horizontal supranuclear gaze palsy that can be subtle and detected only with careful rotational movement assessments[4]. In this situation, the detection of eye movement abnormalities can help differentiate patients with type III (chronic neuronopathic Niemann Pick type C (NPC) is a cholesterol trafficking LSD; the age of presentation is very wide, but the typical eye movement defect is of a vertical supranuclear gaze palsy with paralysis of vertical saccades with sparing of smooth pursuits in the initial stages[5]. This is seen in conjunction with developmental regression and splenomegaly in the early infantile forms, but may be an isolated feature initially in later onset disease.

3. Ptosis

Ptosis can be seen in a wide range of myopathies and myasthenic syndromes. Of the IMD, mitochondrial disorders can present with ptosis that is often worse with fatigue. Of the metabolic myopathies, Pompe disease (glycogen storage disease type II) may have progressive ptosis together with generalized motor and respiratory myopathy, and in infants also hypertrophic cardiomyopathy. Treatment with enzyme replacement therapy is available.

IMDs and the cornea

The cornea may be affected directly or indirectly in many systemic diseases and by many different mechanisms leading to compromise of transparency, optical function, or structural integrity. Inherited disorders of metabolism of proteins, carbohydrates, or lipids can lead to accumulation of substances, which may become

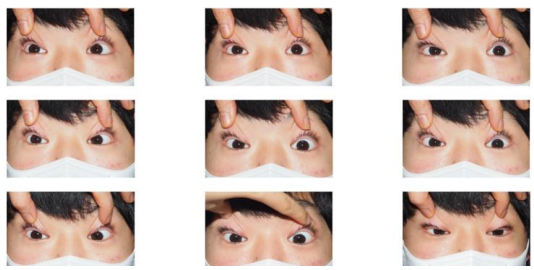

Fig. 1. Ophthalmoplegia and ptosis in chronic progressive external ophthalmoplegia (CPEO) patient.

evident as opacities in the corneal epithelium (ex, Fabry's disease), stroma (ex, cystinosis), or Descemet's membrane (ex, Wilson's disease). Some disorders of protein formation may cause structural abnormalities of the cornea. Accumulation of a metabolic pathway product in the cornea due to enzyme deficiency or mutation of gene encoding the enzyme, leads to staining of the cornea in several IMDs.

2. Keratopathy

Tyrosinaemia type II is a rare amino acid disorder that causes a painful keratitis, resulting in photophobia, lacrimation and burning pain. It is also associated with skin lesions particularly in pressure areas, and also neurodevelopmental delay with microcephaly and seizures in some patients. Slit lamp examination may reveal bilateral herpetic-like lesions with neovascularisation, which untreated can result in corneal scarring. Confirming diagnosis is by identifying very high plasma tyrosine levels and excluding other subtypes of tyrosinaemia[6]. Fabry disease is an X-linked LSD that causes multisystem disease including progressive renal impairment, hypertrophic cardiomyopathy and strokes, although the phenotype is very variable. Females can be affected. Children present with early symptoms of painful acroparaesthesia. Patients may be detected incidentally in a pre-symptomatic stage by the finding of cornea verticallata (corneal whirling); at later stages corneal opacification manifests (Fig. 2). Specific therapy is available with intravenous enzyme replacement, and oral disease modifying drugs, and so early diagnosis is important[7].

2. Corneal clouding/opacification

Corneal clouding and opacification are a feature of several IMD, in particular some of the progressive Lysosomal storage disorders (LSD) conditions, and these should be considered alongside other acquired causes of corneal opacification especially when bilateral. Cystinosis is an LSD caused by a defect in the lysosomal cysteine exporter, and in its severe form causes an early infantile nephropathy with end stage renal failure. Eye involvement is usually at a later stage, and thyroid and gonadal pathology is also expected. There are milder forms isolated to ocular involvement. Cystine deposits accumulate within the stroma of the cornea, iris, lens and retina, and manifest as photophobia with visual defect[8]. Other LSD that presents with corneal clouding included the mucopolysaccharidosis (Fig. 3, ex. MPS I Hurler syndrome, MPS IV (Morquio), MPS VI (Maroteaux Lamy), but not the X-linked MPS II Hunter syndrome), sialic-acid-related LSD (galactosialidosis, sialic acid storage diseases), and other oligosaccharidoses such as alpha-mannosidosis[9]. These are all associated with multisystem disease and progressive dysmorphic features; patients may have

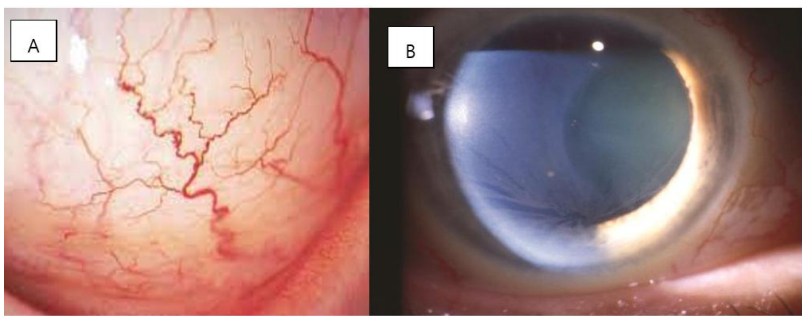

Fig. 2. Conjunctival vessel changes (A) and cornea verticillata (B) in Fabry disease patient.

seen a number of specialists before a diagnosis is reached, emphasizing the need to consider these disorders. In some attenuated forms of MPS, the ocular manifestations may be the initial presenting feature. Lipid-associated disorders can also present with corneal pathology. Tangier disease is a rare disorder affecting cholesterol efflux, associated with orange/yellow tonsils, splenomegaly, peripheral neuropathy and the later development of corneal infiltration.

Another IMD in which recognition of corneal defect is important is Wilson's disease (Fig. 4). Wilson's disease is an inborn error of copper metabolism, having an autosomal recessive inheritance with a mutation in the ATP7B gene encoding a membrane bound copper-transporting ATPase. Its defect leads to increased copper deposition due to impaired biliary copper excretion. There is sunflower cataract and pigmented corneal rings called as Kayser-Fleischer (K-F) rings, due to copper deposit in the outer rim of the cornea[10]. Treatment for Wilson's disease is effective if diagnosis occurs before the onset of life-threatening symptoms.

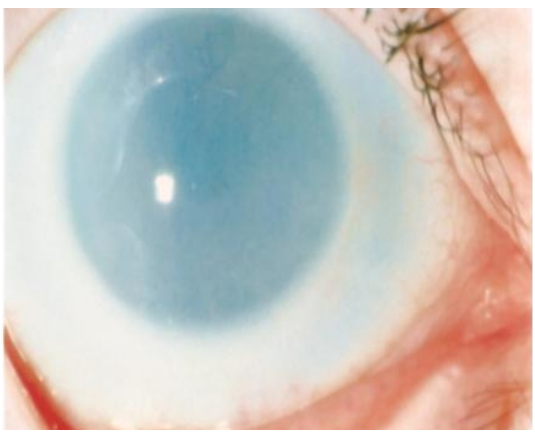

Fig. 3. Corneal clouding in mucopolysaccharidosis patient.

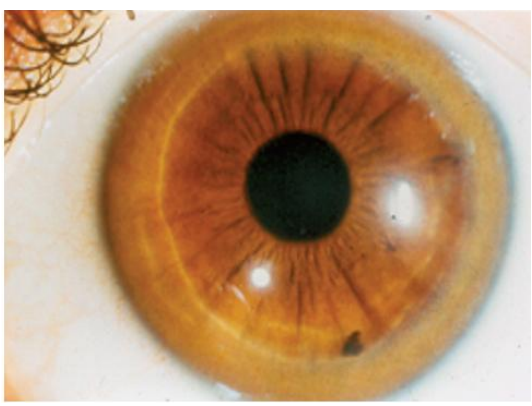

Fig. 4. Cornea deposit in Wilson's disease patient.

IMDs and the Lens

1. Ectopia lentis

Dislocation of the optic lens has a range of causes including Marfan syndrome[11], and the Weill-Marchesani syndromes while metabolic causes include homocystinuria, which is classically associated with downwards-dislocation where this may be the initial presenting feature, and the severe disorder sulfite oxidase deficiency that is associated with early onset seizures (Fig. 5)[12]. Appropriate metabolic screening should be undertaken in patients with unexplained lens dislocation. While homocystinuria is now part of routine new-born screening in many countries, patients born prior to screening may still present symptomatically.

2. Congenital/Juvenile Cataract

The development of congenital and/or juvenile cataract always requires investigation to determine the

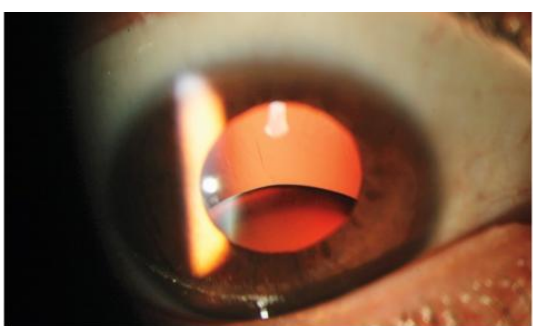

Fig. 5. Ectopic lentis in homocystinuria patient.

etiology (Fig. 6). In many situations, this is a primary genetic disorder affecting the transcription factors such as Pax6, and c-Maf that have pivotal roles in the development of the lens and its polarity[13]. A number of IMD can also present with cataracts, and the age that the cataract develops can help in the differential diagnosis. Truly congenital cataract, that is, those present already at birth, may suggest conditions including Cockayne syndrome which is a DNA repair defect associated with severe short stature, retinitis pigmentosa (RP), sensorineural deafness and early mortality; Lowe syndrome, an X-linked disorder comprising cataracts, proximal renal tubular dysfunction and intellectual impairment due to mutations in the OCRL gene encoding *OCRL-1* which is an inositol polyphosphate 5-phosphatase that has roles in endocytic trafficking; and isolated sorbitol dehydrogenase deficiency specifically affecting the lens[14]. An important category of IMD causing cataracts is the peroxisomal disorders. Peroxisomes are intracellular organelles with a wide range of biochemical functions including beta-oxidation of very long chain fatty acids, alpha-oxidation of phytanic acid, and bile acid and plasmalogen synthesis. Peroxisomal defects include single enzyme defects (such as x-linked adrenoleukodystrophy) or defects affecting the biogenesis of the whole peroxisome (the Zellweger spectrum disorder (ZSD) peroxisomal biogenesis defects)[15]. Patients with ZSD can have congenital cataracts; there are numerous genes involved in peroxisomal biogenesis, and several have been associated with ocular disease including *PEX2*, *PEX11B*, *PEX10*, *PEX12* and *PEX16* [16]. These may even be detected antenatally. Cataract can be the presenting feature, and careful diagnostic work up is required, especially as the classical biochemical biomarker (very long chain fatty acids) may not show consistent abnormalities, such as in patients with *PEX11B*. Later onset cataracts in adulthood can also be due to peroxisomal biogenesis defects, for example, in *PEX7*-related late onset ataxia and cognitive impairment with cataracts. Late (adult) onset cataracts may be seen in several IMD, including in gyrate atrophy of choroid and retina due to ornithine aminotransferase

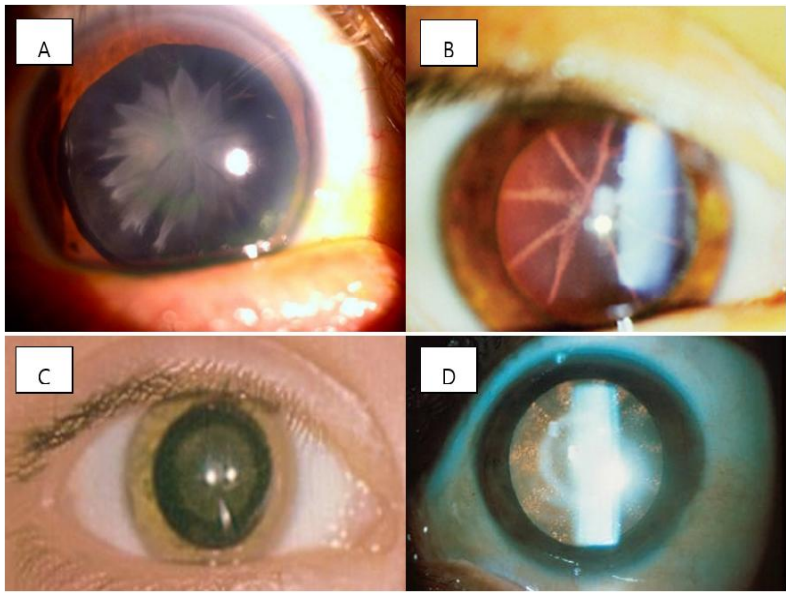

Fig. 6. Various features of congenital/juvenile cataract in inherited metabolic disorders. (A) sunflower cataract, (B) spoke-like cataract, (C) oil-drop cataract, and (D) cataract in Lowe syndrome.

deficiency where posterior capsule cataracts are associated with visual field defects and retinopathy.

Neonatal onset cataracts are a feature of the galactose metabolism disorders. Galactose is derived from the disaccharide lactose, the main carbohydrate in mammalian milk. Lactose is hydrolysed by intestinal lactase generating galactose and glucose which are then absorbed across the brush border by the SGLT1 co-transporter. Galactose is phosphorylated to galactose-1-phosphate by the galactokinase (GALK), and is then converted to uridine diphosphogalactose (UDPgalactose) by galactose-1-phosphate uridyltransferase (GALT or 'Gal-1-put'). UDPgalactose is an important source of galactose for the generation of complex glycoconjugates such as glycoproteins and glycosaminoglycans. Galactose can also be converted to galactitol via aldose reductase; and UDPglucose can be interconverted to UDPgalactose by UDPgalactose-4-epimerase (GALE). Disorders of galactose metabolism are associated with defects in any of these enzymes (GALT/Gal1-put, GALK, epimerase/GALE)[17,18]. Cataract formation in all of the disorders occurs due to the accumulation of galactitol in the crystalline lens. Classical galactosaemia is caused by GALT deficiency, and is associated with very early oil drop cataract; this may resolve spontaneously if treatment with galactose-free diet is introduced promptly, but the cataract may mature and require surgical correction if left untreated. In galactokinase deficiency cataracts are the only clinical feature seen, due to the osmotic effect of galactitol causing swelling of fibers within the lens. In all situations where galactosaemia is suspected, immediate treatment with dietary galactose restriction is mandatory until testing is completed to confirm or refute the diagnosis. Cataracts appearing during infant and childhood may be due to many different IMD. The LSD conditions including alpha mannosidosis, sialidsis and Fabry disease all are associated with cataracts, and would usually be seen in the context of multisystem disease. Vici syndrome, also includes cataracts in its constellation of symptoms Juvenile/adult onset cataracts are seen in cerebrotendinous xanthomatosis (CTX), associated with progressive neurological abnormalities and tendon xanthomata, and Wilson disease can also present with 'sunflower cataracts' as well as the classical Kaiser-Fleischer rings[13].

IMDs and Glaucoma

Raised intraocular pressure may be seen as a secondary feature in several IMD with other ocular pathologies, including in the congenital disorders of glycosylation and the mucopolysaccharidoses[19].

IMDs and Retina

1. Retina Retinitis pigmentosa (RP)

Most cases of RP with loss of retinal photoreceptor cells and pigmentary deposits are caused by primary genetic defects, either autosomal dominant or recessive. However, RP is seen as part of many different IMD. Primary vitamin E malabsorption, or disorders with secondary vitamin E and A deficiency such as abetalipoproteinaemia, cause RP together with other neurological manifestations of vitamin E deficiency. The progression of eye disease in these conditions can be altered with high dose vitamin supplementation. The Cobalamin C defect in the vitamin B12 metabolic pathway is associated with RP, together with multisystem disease including neurological, hematological and cardio-pulmonary features in early onset patients, or a milder phenotype with slower progressing neurological disease with visual loss, although the visual defect may progress despite treatment[20]. Disorders of brain iron accumulation (neurodegeneration with brain iron accumulation [NBIA]) including infantile neuroaxonal dystrophy and pantothenate kinase deficiency

(PKAN) incorporate retinal pathology, with pigmentary retinopathy reported in 58% of early-onset PKAN patients and 15% of late-onset patients (Fig. 7)[21]. Treatments are currently symptomatic only; the diagnosis is often suggested due to specific features on MRI neuroimaging showing iron accumulation in specific brain regions The neuronal ceroid lipofuscinoses (Batten-disease spectrum) conditions have a very important ocular component including RP and progressive optic atrophy, with visual loss being a hallmark of many of the subtypes associated with 13 different genes. Mitochondrial disorders can present with RP with visual failure as a primary feature, for example in neuropathy, ataxia with retinitis pigmentosa (NARP).

2. Cherry red spot

The retinal 'cherry red spot' is a deep red circular area temporal to the optic disc at the central macula, surrounded by a pale 'halo'. The pale halo is caused by accumulation of storage material within the retinal cells which lose their normal transparency, while the foveola which does not contain ganglion cells remains transparent and so the choroid vasculature remains visible and generates the 'red spot'[22]. It is seen as an acquired phenomenon if there is central retinal artery thrombosis, but in children is usually due to an IMD and its identification can help refine the differential diagnosis considerably in a child with multisystem disease. Specifically, several LSDs are associated with the cherry red spot as these conditions result in accumulation of intracellular storage material. These disorders may also have hepatosplenomegaly as in GM1 gangliosidosis, galactosialidosis or Niemann Pick A disease, and dysmorphic facial features may also be evident. Prominent myoclonus or startle response is seen in GM2 gangliosidoses (Tay Sachs and Sandhoff variants).

IMDs and Optic nerve

Optic atrophy (degeneration of the retinal ganglion cells with optic nerve pallor due to deterioration of the optic nerve at any point in its course) can manifest in many IMD[23]. Optic atrophy is an important feature in many of the mitochondrial disorders, including Leber hereditary optic neuropathy (LHON) (Fig 8)[24]. The ocular features of mitochondrial disorders are very diverse, and include as described previously disorders of ocular motor function as well as visual function. The diagnosis of mitochondrial disease can be challenging, given the significant heterogeneity in clinical presentation, time course of disease evolution, and the complex genetics of mitochondrial function. Optic atrophy can be seen in many of the lysosomal disorders including Krabbe and metachromatic leukodystrophy where there is progressive loss of cerebral ne-

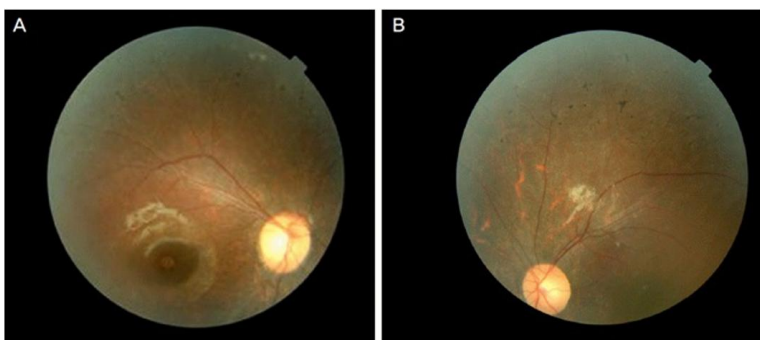

Fig. 7. Fundus finding o the right eye (A) and the left eye (B). Including retinitis pigmentosa and optic atrophy, of pantothenate kinase deficiency (PKAN)

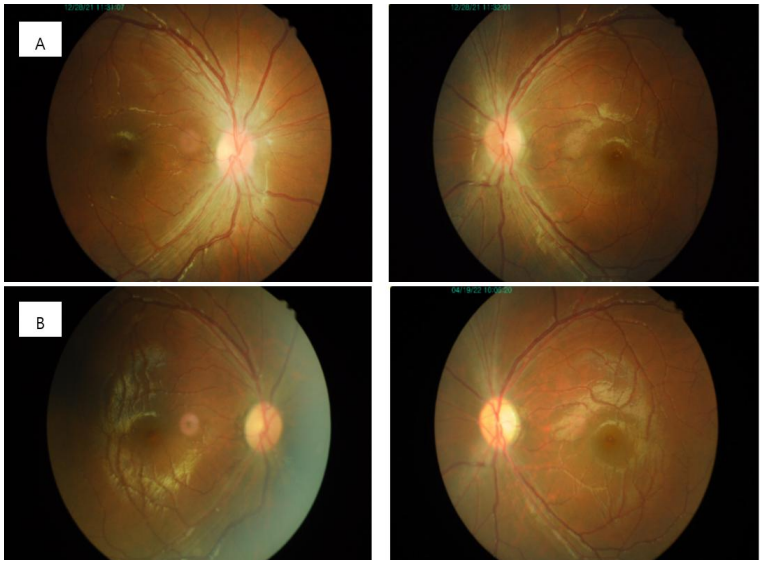

Fig. 8. Optic disc changes in the Leber hereditary optic neuropathy (LHON) patient. Optic disc swelling in early stage (A) changed to optic atrophy in the late state (B).

rvous tissue, the peroxisomal biogenesis disorders and X-linked adrenoleukodystrophy[2].

Conclusion

This review has summarized some of the many IMD that can present initially, or subsequently, with ophthalmic involvement. We would like to highlight that early diagnosis of an IMD may be made if this is considered in the differential diagnosis of the ophthalmic features, which may facilitate earlier systemic treatment and save the vision. A combined approach and management by an ophthalmologist, pediatrician, biochemist, and medical geneticist is essential to successfully treat IMD patients.

References

1) Rajappa M, Goyal A, Kaur J. Inherited metabolic disorders involving the eye: A clinico-biochemical perspective. Eye 2010;24:507-18.
2) Davison JE. Eye involvement in inherited metabolic disorders. Ther Adv Ophthalmol 2020;12:251584142097910.
3) Eklund EA, Freeze HH. The congenital disorders of glycosylation: a multifaceted group of syndromes. NeuroRx 2006;3:254-63.
4) Harris CM, Taylor DS, Vellodi A. Ocular motor abnormalities in Gaucher disease. Neuropediatrics 1999;30:289-93.
5) Blundell J, Frisson S, Chakrapani A, Gissen P, Hendriksz C, Vijay S, et al. Oculomotor abnormalities in children with Niemann-Pick type C. Mol Genet Metab 2018;123:159-68.
6) Rabinowitz LG, Williams LR, Anderson CE, Mazur A, Kaplan P. Painful keratoderma and photophobia: hallmarks of tyrosinemia type II. J Pediatr 1995;126:266-9.
7) Mehta A, Beck M, Eyskens F, Feliciani C, Kantola I, Ramaswami U, et al. Fabry disease: a review of current management strategies. QJM 2010;103:641-59.
8) Dureau P, Broyer M, Dufier JL. Evolution of ocular manifestations in nephropathic cystinosis: a long-term study of a population treated with cysteamine. J Pediatr Ophthalmol Strabismus 2003;40:142-6.
9) Ferrari S, Ponzin D, Ashworth JL, Ashworth JL, Fahnehjelm KT, Summers CG, et al. Diagnosis and management of ophthalmological features in patients with mucopolysaccharidosis. Br J Ophthalmol 2011;95:613-9.
10) Ram J, Gupta A. Kayser-Fleischer ring and sunflower cataract in Wilson disease. JAMA Ophthalmol 2014;

132:873.
11) Esfandiari H, Ansari S, Mohammad-Rabei H, Mets MB. Management Strategies of Ocular Abnormalities in Patients with Marfan Syndrome: Current Perspective. J Ophthalmic Vis Res 2019;14:71-7.
12) Rahman M, Sharma M, Aggarwal P, Singla S, Jain N. Homocystinuria and ocular complications - A review. Indian J Ophthalmol 2022;70:2272-8.
13) Khokhar SK, Pillay G, Dhull C, Agarwal E, Mahabir M, Aggarwal P. Pediatric cataract. Indian J Ophthalmol 2017;65:1340-9.
14) Vetter V, Shin YS. Lens sorbitol dehydrogenase deficiency in a patient with congenital cataract. Eur J Pediatr 1995;154:389-91.
15) Shen O, Michaelson-Cohen R, Gross-Tsur V, Eilat A, Yanai N, Green T, et al. Prenatal observation of nystagmus, cataracts, and brain abnormalities in a case of Zellweger spectrum disorder syndrome. Prenat Diagn 2016;36:894-5.
16) Bose M, Yergeau C, D'Souza Y, Cuthbertson DD, Lopez MJ, Smolen AK, et al. Characterization of Severity in Zellweger Spectrum Disorder by Clinical Findings: A Scoping Review, Meta-Analysis and Medical Chart Review. Cells 2022;11.
17) Chhapan RJ, Yerramneni R, Ramappa M. Diagnosing the oil drop: A case report and review of the literature. Indian J Ophthalmol 2019;67:1705-6.
18) Beigi B, O'Keefe M, Bowell R, Naughten E, Badawi N, Lanigan B. Ophthalmic findings in classical galactosaemia--prospective study. Br J Ophthalmol 1993;77:162-4.
19) Tomatsu S, Pitz S, Hampel U. Ophthalmological Findings in Mucopolysaccharidoses. J Clin Med 2019;8
20) Huemer M, Diodato D, Schwahn B, Schiff M, Bandeira A, Benoist, JF, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis 2017;40:21-48.
21) Chang X, Zhang J, Jiang Y, Wang J, Wu Y. Natural history and genotype-phenotype correlation of pantothenate kinase-associated neurodegeneration. CNS Neurosci Ther 2020;26:754-61.
22) Chen H, Chan AY, Stone DU, Mandal NA. Beyond the cherry-red spot: Ocular manifestations of sphingolipid-mediated neurodegenerative and inflammatory disorders. Surv Ophthalmol 2014;59:64-76.
23) Davison JE, Rahman S. Recognition, investigation and management of mitochondrial disease. Arch Dis Child 2017;102:1082-90.
24) Davila-Siliezar P, Carter M, Milea D, Lee AG. Leber hereditary optic neuropathy: new and emerging therapies. Curr Opin Ophthalmol 2022;33:574-8.