

Ocular Manifestations of Pediatric Systemic Disease

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Pediatric diseases are important because diagnosis and care for these can be complex. Among them, specific diseases have been associated with ocular involvement. This review presents the ocular manifestations of various pediatric diseases relevant to the clinician. An array of ocular manifestations of hyperthyroidism, hypoparathyroidism, diabetes mellitus, porphyria, cystinosis, mucopolysaccharidosis, Wilson disease, juvenile idiopathic arthritis, systemic lupus erythematosus, Marfan syndrome, Weill-Marchesani syndrome are described. In this review we will review ocular manifestations of systemic pediatric diseases for comprehensive understanding of eye involvement. With this review, authors can recognize the ocular manifestations for diagnosis and management of pediatric systemic diseases.

Key Words: Ocular Manifestation; Pediatrics

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INTRODUCTION

An ocular manifestation of a systemic disease is an ocular condition that directly or indirectly results from a pathologic process from another part of the body. Ocular manifestations can occur in various systemic diseases in pediatrics. However, ocular manifestations are difficult to recognize especially in pediatric diseases because most clinicians ignore ocular involvement of systemic diseases. Ocular manifestations can be the first findings of systemic disease in some pediatric disease, and numerous ocular manifestations can be associated with amblyopia, which is a disorder of sight. Therefore we must be able to recognize the ocular manifestations for diagnosis and management of pediatric systemic diseases.

Although we cannot deal with ocular manifestations of all pediatric systemic disease in this paper, we have reviewed particular diseases that are may be of interest to the general physician and pediatric ophthalmologists. This paper aims to review the ocular manifestations of various pediatric diseases.

HYPERTHYROIDISM

Hyperthyroidism is caused by over secretion of thyroid hormone; during childhood, it is caused by Graves' hyperthyroidism, the most common cause of pediatric hyperthyroidism [1]. In children, the incidence of Graves' disease is about 1:10,000 [2]. Graves' hyperthyroidism is an autoimmune disorder; secretion of thyroid-stimulating immunoglobulin that binds to and triggers the G-protein-coupled thyroid-stimulating hormone (TSH) receptor results in diffuse enlargement of the thyroid gland. Other etiologies of hyperthyroidism include gain-of-function germline mutations in the TSH receptor, which are detected in both familial and sporadic cases of non-autoimmune hyperthyroidism. These subjects, whose disease can occur in the infantile period or in later childhood, have a hyperplastic thyroid gland with goiter and decreased levels of TSH.

Childhood onset Graves' ophthalmopathy is uncommon and occurs mostly in girls. Common aspects are edema of eyelid, lid lag, and lagophthalmos. Mild proptosis and conjunctival associa-

tion occurs in about 10%. CT Scanning or ultrasound may show enlarged extraocular muscles, but significantly limitation of ocular movement is rare and visually threatening problems have not been reported [3]. The condition generally shows a good prognosis for spontaneous resolution, usually without recurrence or need for major intervention such as intravenous steroids or decompression of orbit [4].

HYPOPARATHYROIDISM

Hypocalcemia is a common metabolic problem in newborns, and is usual in neonates which presents within 72 hours, especially in prematurity, in neonates with asphyxiation, and in infants of diabetic mothers. After the 2nd-3rd day and during the first week, the degree of serum calcium is determined by the type of feeding (late neonatal hypocalcemia) [5]. In these neonates with hypocalcemia, the function made by the parathyroid glands remains to be verified.

There is a spectrum of deficient parathyroid with clinical signs varying from asymptomatic to those of longstanding status [6]. Mild insufficiency may be detected only by adequate research results. Cataracts in infants with complete disorders are a direct result of hypoparathyroidism [7]; other autoimmune eye disorders such as keratitis and conjunctivitis can also appear [8].

DIABETES MELLITUS

Pediatric diabetes mellitus was mostly considered as the type 1 insulin-dependent form, until recently [9]. With increasing weight gain in the pediatric population however, type 2 diabetes and insulin resistance now stands as an emerging epidemic in children and adolescents, resulting 8-45% of all juvenile diabetes [10]. Initial screening of pediatric diabetic patients by eye doctors between 3-5 years following diagnosis remains critical.

Opacities of lens occur infrequently in children with diabetes mellitus. When they do develop, they usually appear in the teenage years. They frequently start as cortical opacities but may rapidly progress to total lens opacities. Diabetic retinopathy, while rare in children, is strongly correlated with duration of diabetes and overall control of glucose. The prevalence of diabetic retinopathy rises consistently following puberty, with a 4.8 times greater risk of postpubescent adolescents developing diabetic retinopathy relative to pubescent or pre-pubescent children with the same du-

ration of diabetes [11].

PORPHYRIA

Porphyrias are a group of rare diseases in which chemical substances called porphyrins accumulate resulting from alteration of the enzymes that transform the various porphyrins into others [12]. These enzymes are most abundant in the blood, bone marrow, and liver. Erythropoietic porphyrias usually exist at birth or early infancy with cutaneous photosensitivity, or in the situation of congenital erythropoietic porphyria (CEP), even in non-immune hydrops fetalis in utero. Erythropoietic protoporphyria (EPP) is the most interesting pathophysiology (or phenomenon) to pediatricians.

Phototoxic changes of the lids, the conjunctiva and the sclera show the fundamental pathological mechanism leading to clinical manifestations in CEP. Contracture of the lids may result in incomplete closure of eyelids with unhealed keratitis and severe aggravation of light induced change to conjunctiva and sclera [13].

CYSTINOSIS

Cystinosis is a rare disorder caused by a failure in the metabolism of cysteine that results in deposit of cystine crystals in the major parts of the body, mainly the kidney, liver, eye, and brain [14]. Ocular manifestations include photophobia, retinal disorder, and loss of vision.

MUCOPOLYSACCHARIDOSIS

Mucopolysaccharidoses are genetic, progressive disorders caused by mutations of chromosomes coding for lysosomal enzymes needed to degrade glycosaminoglycans (acid mucopolysaccharides). Glycosaminoglycans (GAGs) are long-chain complex carbohydrates comprised of uronic acids, amino sugars, and neutral sugars [15].

The corneas take on a "ground glass" shape that, in some instances is better seen with light illumination than on slit-lamp microscopy. Degeneration of retina is seen in most forms, not in Morquio disease. Its insidious onset is usually overshadowed by the opacities of the cornea. Some children may show night-blindness or dimness with blurring of the cornea. Glaucoma probably occurs in all of the mucopolysaccharidoses and some other metabol-

ic diseases with opacity of corneas.

WILSON DISEASE

Wilson disease usually shows either with liver disorder at 5-20 years of age or with neurological symptoms, typically between 20-40 years, but sometimes during in childhood [16]. Liver manifestations include chronic active hepatitis, cirrhosis and fulminant hepatic failure. Deposition of copper in peripheral corneal Descemet's membrane was detected as golden brown pigmentations: the Kayser-Fleischer ring [17].

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile rheumatoid arthritis, also known as juvenile idiopathic arthritis, is the most common type of arthritis in children under the age of 17 [18]. JIA is comprised of a heterogeneous group of several disease subtypes. The cause and pathology of JIA are mostly unknown, and the hereditary portion is difficult, making complete differentiation among various subtypes complex.

Treatment of JIA must comprise periodic ocular microscopic examinations to detect for asymptomatic anterior uveitis. Optimal management of uveitis requires coordination between the eye doctor and rheumatic clinician. The initial treatment of uveitis may include cycloplegics and corticosteroids, or subconjunctival drug delivery. Disease-modifying antirheumatic drugs create limitations in high usage of steroids, and an antimetabolite and antifolate drug are usable in managing untreatable uveitis. In those aggravating uveitis, arthritis occurs at 28 months and uveitis 13 months later: 86% have oligoarticular onset juvenile arthritis, 75% are girls, and 80% present of ANA [19].

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE), also known simply as lupus, is an autoimmune disorder characterized by multiorgan inflammation and the existence of various autoantibodies [20]. SLE can appear in pediatrics and adolescents, especially affecting women of reproductive age. Although most body parts may be influenced, SLE is a chronic inflammatory connective tissue disorder that can involve joints, kidneys, skin, mucous membranes, and blood vessels, and the central nervous system [21].

The vasculopathy associates small arteries, arterioles, and capil-

laries, resulting in fibrinoid necrosis. Hypersensitivity vasculitis was detected in 28% of cases. Thrombosis is more likely found in the existence of anticardiolipin autoantibodies, and these may also occur as a separate phenomenon in the antiphospholipid syndrome, or precede the occurrence of SLE for several years. CNS disease may be involved by diffuse vasculopathy and localized thrombosis exacerbated by the presence of anticardiolipin autoantibodies.

Five percent of pediatrics with SLE has eye involvement. The most frequent eye involvement is dry eye: however, chronic inflammation of cornea and conjunctiva is uncommon. Lupus retinopathy is a mark of severe diffuse vasculopathy and may be involved by simultaneous hypertensive changes. Scleritis, episcleritis, and keratitis are rare and may indicate uncontrolled systemic disease.

MARFAN SYNDROME

Marfan syndrome (MFS) is a genetic, systemic, connective tissue disorder from mutations in the FBN1 or fibrillin gene on chromosome 15 [22]. It primarily involves the skeletal, ocular, and cardiovascular systems.

Displacement or malposition of the crystalline lens occurs in approximately 60-70% of subjects, although it is not essential in the disorder. Other ocular manifestations include early and severe nearsightedness, corneal flattening, and high myopia, iris hypoplasia, and hypoplastic ciliary muscle, causing impaired constriction of the pupil. Patients are vulnerable to retinal tear and early opacity of lens or glaucoma. Early ectopia lentis can be detected as a flattening or scalloped notching of one lens sector. Zonular fibers typically elongate and the ability of accommodation may be unaffected. Progression of ectopia lentis is relatively uncommon [23].

WEILL-MARCHESANI SYNDROME

Weill-Marchesani syndrome is an uncommon systemic connective tissue disease. Affected patients exhibit microspherophakia, ectopia lentis, lenticular myopia, and glaucoma in conjunction with short stature, brachydactyly, and joint stiffness [24]. As well as FBN1 mutations (type 2), the syndrome may be originated from homozygous or compound heterozygous mutations in ADAMTS10 (type 1) or homozygous mutations in LTBP2 (type 3).

CONCLUSIONS

This comprehensive review paper describes a short but complete guide to ocular involvement of various pediatric diseases. An ocular manifestation of a pediatric systemic disease can be its first visible presentation, and the eye can provide clues for diagnosis of systemic diseases. For the proper diagnosis and management of pediatric systemic diseases, we need to pay attention to the involved ocular manifestations.

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