Review Article

The eye as a window to rare endocrine disorders

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ABSTRACT

The human eye, as an organ, can offer critical clues to the diagnosis of various systemic illnesses. Ocular changes are common in various endocrine disorders such as diabetes mellitus and Graves' disease. However there exist a large number of lesser known endocrine disorders where ocular involvement is significant. Awareness of these associations is the first step in the diagnosis and management of these complex patients. The rare syndromes involving the pituitary hypothalamic axis with significant ocular involvement include Septo-optic dysplasia, Kallman's syndrome, and Empty Sella syndrome all affecting the optic nerve at the optic chiasa. The syndromes involving the thyroid and parathyroid glands that have ocular manifestations and are rare include Mc Cune Albright syndrome wherein optic nerve decompression may occur due to fibrous dysplasia, primary hyperparathyroidism that may present as red eye due to scleritis and Ascher syndrome wherein ptosis occurs. Allgrove's syndrome, Cushing's disease, and Addison's disease are the rare endocrine syndromes discussed involving the adrenals and eye. Ocular involvement is also seen in gonadal syndromes such as Bardet Biedl, Turner's, Rothmund's, and Klinefelter's syndrome. This review also highlights the ocular manifestation of miscellaneous syndromes such as Werner's, Cockayne's, Wolfram's, Kearns Sayre's, and Autoimmune polyendocrine syndrome. The knowledge of these relatively uncommon endocrine disorders and their ocular manifestations will help an endocrinologist reach a diagnosis and will alert an ophthalmologist to seek specialty consultation of an endocrinologist when encountered with such cases.

Key words: Endocrine syndromes, ocular manifestations, visual acuity

Introduction

A syndrome is a term used to correlate a number of apparently unrelated conditions that have a tendency to appear together to form a composite picture. The eye can be affected in a number of systemic diseases. The list of endocrine disorders involving the eye is endless. Some of the common endocrine diseases where eye involvement is significant include diabetes mellitus and Graves' ophthalmopathy, though these are not discussed as these fall outside the scope of this review**.** However, they have been well reviewed in recent publications.[1,2] However, there exist a large number of lesser known endocrine disorders where eye involvement is significant. This review is an attempt to highlight the ocular manifestations of some of the uncommon endocrine disorders.

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Hypothalamic – Pituitary Syndromes

Septo-optic dysplasia (SOD): Septo-optic dysplasia, previously termed *de Morsier syndrome* was first described by Reeves in 1941 as an absence of the septum pellucidum with associated optic abnormalities.[3] Subsequently an association with pituitary dysfunction was also described.[4] It is a rare congenital anomaly, equally prevalent in males and females, with a reported incidence of 1 in 10 000 live births.[5]

The classical triad of SOD includes (i) optic nerve hypoplasia (ii) pituitary hormone abnormalities (iii) midline brain defects, including agenesis of the septum pellucidum and/or corpus callosum.[6] Diagnosis of SOD can be made clinically when two or more features of the triad are present.

The main reported clinical findings of SOD are

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hypopituitarism (62–80%), with growth hormone deficiency being the commonest endocrine abnormality, visual impairment (23% having significant visual impairment), and developmental delay. The latter is more common in children with bilateral (57%) as compared to unilateral (32%) optic nerve hypoplasia.[7] Seizures, developmental delay and cerebral palsy are the most frequent neurological associations.[8]

Ocular manifestations: A child with SOD may have varying degrees of visual impairment. The presence of strabismus or nystagmus in a child at birth with multiple congenital abnormalities should alert an ophthalmologist to seek the opinion of an endocrinologist. The other ocular features of SOD include microphthalmia or anophthalmia, optic nerve dysplasia, or hypoplasia (wherein the optic nerve appears small and pale).[9]

Kallman's syndrome: Kallman's syndrome is a rare genetic disorder due to abnormal migration of olfactory axons and gonadotrophin releasing hormone producing neurons. It consists of defective gonadotropin-releasing hormone synthesis with olfactory nerve agenesis or hypoplasia and variable anosmia. The inheritance of Kallman's syndrome may be X-linked, autosomal recessive or autosomal dominant with variable penetrance.[10]

Clinical features include hypogonadotrophic hypogonadism with anosmia. Associated defects inconsistently present include cleft lip, cleft palate, imperfect facial fusion, seizure disorder, short metacarpals, pes cavus, neurosensory loss, and cerebellar ataxia.[11]

Ocular manifestations: Patients with Kallman's syndrome can have associated optic atrophy [Figure 1], color blindness and oculomotor abnormalities.[12]

Empty sella syndrome: Empty sella turcica is defined as an intrasellar herniation of the suprasellar space with compression of the pituitary gland producing a remodeling of sella that results from a combination of incomplete diaphragma sella and an increased CSF fluid pressure in many cases.[13] Empty sella is classified as primary when it occurs in persons who have not received pituitary radiation or pituitary surgery, while an empty sella discovered following such procedures is classified as secondary sella. Persons with primary empty sella are usually asymptomatic and the detection of this abnormality may be incidental. These patients may sometimes present with headache and hypertension.[13] Upto 50% of patients have associated benign intracranial hypertension.[14]

Ocular manifestations: Ocular findings in patients with primary empty sella include diminished visual acuity and visual field defects such as peripheral field constriction, bitemporal hemianopia, or quadrantanopia. Patients with secondary empty sella predominantly present with visual abnormality occurring due to arachnoidal adhesions and traction on the optic chiasma. They may have an initial improvement in visual symptoms following surgery followed by recurrence of symptoms due to the development of empty sella. On the other hand, some patients who do not have visual symptoms initially may present with a fresh onset of these symptoms.[13]

Oliver Mcfarlane syndrome: Oliver Mcfarlane is an extremely rare condition associated with chorioretinal degeneration, dwarfism with growth hormone deficiency, hair abnormalities, and cerebellar dysfunction.

Ocular manifestations: patients usually present with marked decrease in vision. There is marked chorioretinal degeneration with pigment clumping in the midperiphery.[15]

Von Recklinghausen's disease (Neurofibromatosis 1)(NF1): Neurofibromatosis is an inherited disorder of the neuroectodermal system resulting in hamartomas, particularly of the skin, eyes and nervous system that increase in number and size throughout life. NF1 is inherited as an autosomal dominant disorder. It occurs in 0.05% of the population with a prevalence estimated to be 1 in 3000.[16]

NF1 is characterized by multiple pigmented areas and overgrowth of nerve sheaths and fibrous tissue elements. Multiple café au lait spots are seen. Delayed or true precocious puberty may develop in some cases. Growth hormone deficiency is possible at presentation, but after radiation therapy for associated optic glioma, growth hormone, TSH, ACTH, and gonadotrophin deficiency may develop.[17]

Ocular manifestations: Ocular manifestations of NF1 include iris hamartomas also known as Lisch nodules. Most of the visual morbidity related to this disorder is secondary to the frequent occurrence of optic pathway gliomas in these patients. Most optic gliomas appear in first decade, but only 20–30% become symptomatic.[18] They manifest as unilateral decreased visual acuity or strabismus. Affected individuals may have signs of mild proptosis or optic atrophy. Chiasmal and hypothalamic extension of optic nerve gliomas have also been reported in the literature.[19] Other ocular manifestations include plexiform neurofibromas of the upper lid, congenital glaucoma, and choroidal and retinal hamartomas.

Thyroid – Parathyroid Disorders

McCune Albright syndrome

McCune Albright syndrome is classically defined by the triad of fibrous dysplasia of the bones, café-au-lait skin spots and precocious puberty. It has an estimated prevalence of 1/100 000 and 1/1000 000 and manifests in childhood and young adults.[20] Autonomous hyperfunction most commonly involves the ovary, but other endocrine involvements include thyroid (nodular hyperplasia with thyrotoxicosis), adrenals (multiple hyperplastic nodules with Cushing's syndrome), pituitary (adenoma or hyperplasia), and parathyroid (adenomas or hyperplasia with hyperparathyroidism).

Ocular manifestations: ocular findings appear due to optic nerve compression caused by craniofacial fibrous dysplasia involving the optic canal.[21] Visual field defects, diminished color vision, decreased visual acuity and in long-standing optic nerve compression optic atrophy results.

Primary hyperparathyroidism primary hyperthyroidism may also sometimes present with significant ocular manifestations. The commonly described ocular manifestations of hyperparathyroidism include band keratopathy, asymptomatic conjunctival calcification, and conjunctivitis. Scleritis presenting as red eye has also been reported as a manifestation of hypercalcemia[22] [Figure 2].

Ascher syndrome

Ascher syndrome presents as a combination of blepharochalasis, double lip and nontoxic thyroid enlargement.[23] Ascher syndrome like any other syndromes, rarely has all components together at presentation. Enlargement of the thyroid is present in only 10–50% cases of Ascher syndrome.[24]

Ocular manifestations: blepharochalasis [Figure 3] is present in more than 80% cases. It starts at puberty and usually both upper eyelids are involved. Pathologically it is a form of localized angioedema with decrease in dermal elastin. It is characterized by three stages – first stage or edema stage presents with an intermittent painless swelling of lids.[25] Second stage or atonic ptosis stage presents with ptosis due to dehiscence of levator aponeurosis. Third stage or ptosis adiposa present with medial fat pad atrophy, orbital fat prolapsed, and lacrimal gland prolapse.

Disorders of the Adrenal Glands

1. *Triple a syndrome (Allgrove's syndrome):* triple a syndrome is a rare, autosomal recessive disorder characterized by adrenocorticotrophic hormone (ACTH) resistant adrenal insufficiency, alacrima, achalasia of the esophageal cardia, progressive neurological degeneration, and occasionally autonomic instability.[26] Alacrima is the first and most consistent feature of this syndrome.[27] Other features include achalasia cardia, ACTH-resistant adrenal insufficiency, dwarfism, microcephaly, autonomic dysfunction, progressive neurological degeneration, and chronic symptomatic neutropenia.[28]
   Ocular manifestations: the ophthalmic manifestations of triple A syndrome include alacrima (which is tested by performing Schirmer's test), keratoconjunctivitis sicca, corneal melting, lacrimal gland atrophy, pupillary abnormalities including sluggish pupils, tonic pupils with hypersensitivity to dilute miotics like 0.125% pilocarpine, accommodative dysregulation, amblyopia, and optic atrophy.[26] Lacrimation (both reflex and basal), pupillary miosis, and accommodation are under parasympathetic control. Autonomic dysfunction at the level of the lacrimal gland and pupil explain the ocular abnormalities seen in triple A syndrome.[29]
2. *Cushing syndrome:* cushing syndrome comprises the signs and symptoms associated with prolonged exposure to inappropriately elevated levels of free plasma glucocorticoids. Cushing's syndrome is common, occurring to some degree in majority of patients taking long term corticosteroid therapy. Endogenous causes of Cushing's syndrome are rare and result in loss of the normal feedback mechanism of the hypothalamic pituitary axis and the normal circadian rhythm of cortisol secretion.[30]
   Ocular manifestations: ocular effects of Cushing's syndrome include raised intraocular pressure[31] and exophthalmos[32] (seen in up to one third of patients in Cushing's original series), the latter occurring due to increased retro-orbital fat deposition. Cataracts occur as a complication of long term corticosteroid therapy.
3. *Addison's disease:* Addison's disease is characterized by primary hypoadrenalism, the etiology of which could be autoimmune, infectious, and secondary to infiltrations or due to congenital adrenal hypoplasia. The clinical features of chronic adrenal insufficiency include weakness, fatigue, tiredness, gastrointestinal symptoms like nausea, vomiting, abdominal pain and diarrhea, salt craving, and joint pains.
   Ocular manifestations: ocular manifestations though rare in Addison's disease include ptosis, blepharitis, blepharospasm, keratoconjunctivitis with extreme photophobia, corneal ulcers, episcleritis, cataract, and papilloedema.[33]

Gonadal Disorders

1. *Bardet–Biedl syndrome*: Bardet–Biedl syndrome is an autosomal recessive condition with a wide spectrum of clinical features. The important clinical features of this condition are rod cone dystrophy, postaxial polydactyly, central obesity, mental retardation, hypogonadism, and renal dysfunction.[34] Other features, not always present include hepatic fibrosis, diabetes mellitus, reproductive abnormalities, short stature, developmental delays, and speech deficits. Bardet–Biedl syndrome is distinguished from the much rarer Laurence Moon syndrome in which retinal pigmentary degeneration, mental retardation, and hypogonadism occur in conjunction with progressive spastic paraparesis and distal muscle weakness but without polydactyly.[35]
   Ocular manifestations: the principal ocular manifestation is a rod cone dystrophy or atypical retinitis pigmentosa. This is a universal finding among all adults diagnosed with Bardet–Biedl syndrome, but symptoms do not appear until 8 years of age and signs are often not visible till early teens.[35] These patients present with night blindness and a generalized constriction of the visual fields. The other ocular associations that help to suggest the diagnosis include myopia, strabismus, and cataract in young adults.[36]
2. *Turner syndrome:* Turner syndrome is a condition in which there is an absence or structural abnormality of one X chromosome in phenotypic females. The cardinal features of Turner syndrome are short stature, left-sided congenital heart defects, and ovarian dysgenesis. The incidence of the syndrome is estimated to be 1 in 3000 live births.[37]
   Ocular manifestations: the common ocular findings in Turner syndrome include strabismus, ptosis, hypertelorism, epicanthus, and red–green color deficiency.[38] Ocular hypertension and glaucoma have also been reported in patients with Turner syndrome.[36] Lyod *et al.*, reported anterior segment dysgenesis in the form of iris hypoplasia, trabeculodysgenesis and Reiger's anomaly (iridocorneal dysgenesis) in patients with mosaic Turner syndrome.[39]
3. *Rothmund syndrome:* Rothmund syndrome is an autosomal recessive disorder, more commonly seen in females. It is a genodermatosis presenting with a characteristic facial rash (poikiloderma), hypogonadism, hypomenorrhoea, skeletal head deformity (enlarged head with depressed nasal bridge as well as microcephaly), small stature, short or malformed distal phalanges, radial ray defects, premature ageing and a predisposition to cancer.[40]
   Ocular manifestations: the ocular findings in patients with Rothmund syndrome include sparse or absent eyebrows and hypertelorism.[41] Bilateral cataracts [Figure 4] are a common ocular feature of this syndrome.[42] Isolated cases of bilateral glaucoma, retinal coloboma, and chorioretinal atrophy have also been documented in the literature.[41]
4. *Klinefelter's syndrome:* Klinefelter's syndrome is the most frequent form of sex chromosome aneuploidy with a reported incidence of between 1 : 500 and 1 : 1000 live births.[43] The clinical features of Klinefelter's syndrome and its variants include small testis, azoospermia, hypoandrogenemia, tall stature and increased leg length, increased incidence of learning difficulties, obesity, breast tumors, varicose veins, and impaired glucose tolerance.[44]
   Ocular manifestations: ocular findings associated with Klinefelter's syndrome include colobomas of the iris, choroid and optic nerve, microphthalmia, and strabismus[45] [Figures 5, 6a and b]. Cases of high myopia also have been reported in association with 49, XXXXY syndrome, a variant of Klinefelter's syndrome.[46]

Miscellaneous Syndromes

1. *Werner syndrome:* Werner syndrome is characterized by premature ageing associated with graying of hair before the age of 20 years. Other associations of this syndrome include diabetes mellitus type 2, osteoporosis and atherosclerosis. Malignancy (sarcomas) occurs in 10% of the cases.[47]
   Ocular manifestations: bilateral cataracts are diagnosed at a median age of 30 years.[48] These cataracts have been described as subcapsular, cortical, nuclear, zonular or with punctate opacifications.[49] Bullous keratopathy is a common postoperative complication in these cases and may necessitate penetrating keratoplasty.[50]
2. *Cockayne syndrome:* Cockayne syndrome is a progressive neurological disorder characterized by growth failure in infancy (cachectic dwarfism), deficient neurological development, progressive retinal degeneration, and extreme sensitivity to sunlight.[51]
   Ocular manifestations: one of the hallmarks of Cockayne syndrome is pigmentary degeneration of the retina [Figure 7]. It occurs in a high percentage of reported cases (60–100%).[52] Most often a salt and pepper type fundus appearance is noted and the changes are progressive throughout life. Electroretinogram (ERG) shows variable degrees of reduction in scotopic and photopic responses.[52] Other anterior segment findings include cataract, microphthalmia, iris hypoplasia, and enophthalmos.[53]
3. *Kearns Sayre syndrome (chronic progressive external*

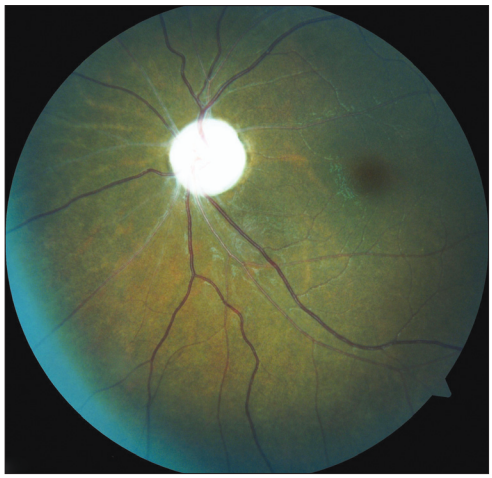

Figure 1: Optic atrophy

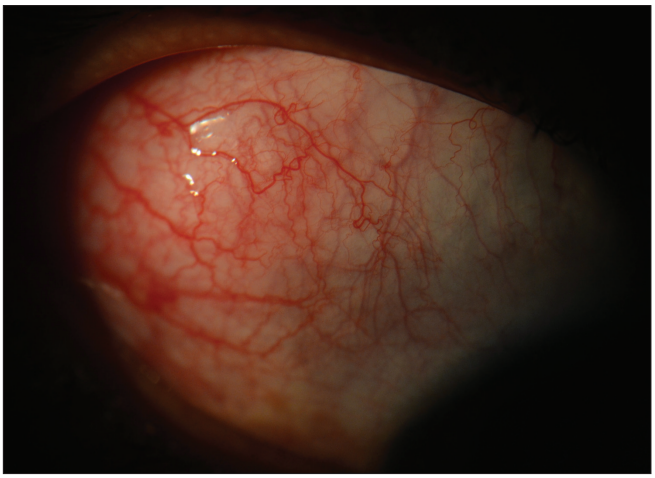

Figure 2: Scleritis

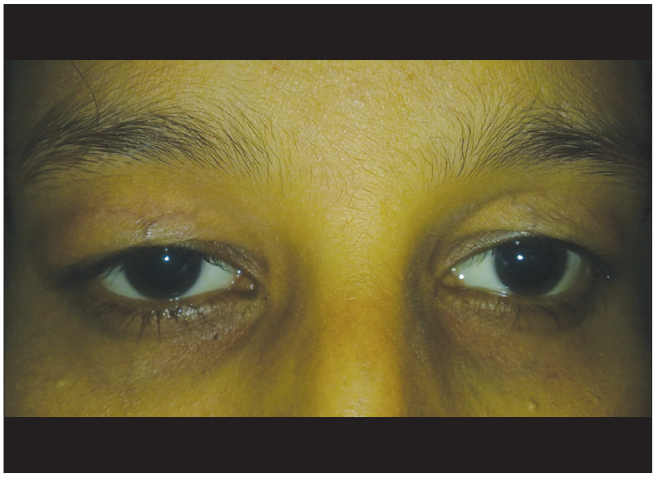

Figure 3: Blepharochalasis

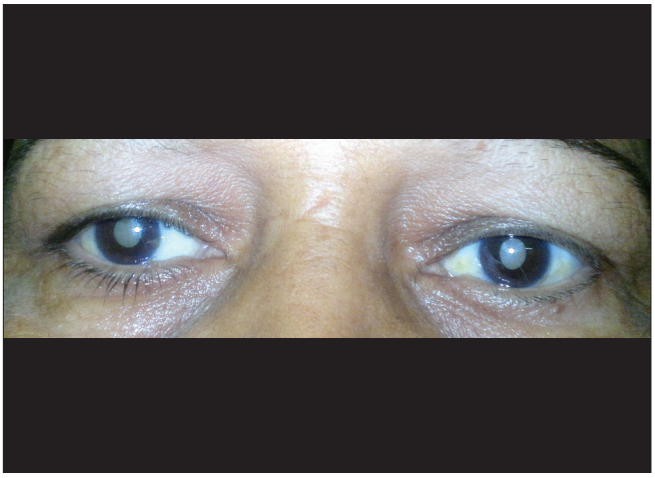

Figure 4: Bilateral cataract

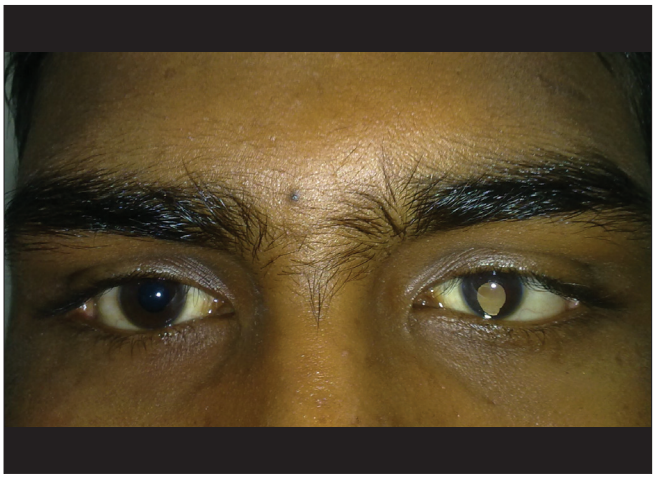

Figure 5: Microphthalmos with strabismus and iris coloboma

ophthalmoplegia): it is characterized by myopathic abnormalities leading to ophthalmoplegia and progressive weakness with severe endocrine abnormalities. Endocrine abnormalities in Kearns Sayre syndrome include hypoparathyroidism, primary gonadal failure, diabetes mellitus, and hypopituitarism.[54]

Ocular manifestations: bilateral sometimes asymmetric ptosis is usually the first sign of Kearns Sayre syndrome, often beginning before adolescence.[55] This is followed within a few years by progressive external ophthalmoplegia. Eventually weakness of the orbicularis oculi and other facial muscle also results. Pigmentary retinopathy is another feature of this syndrome. This is different from retinitis pigmentosa in that it typically involves the posterior pole and bony spicule formation is uncommon.

4. *Wolfram syndrome:* it is a rare autosomal recessive disorder also called DIDMOAD (diabetes insipidus, diabetes mellitus, progressive bilateral optic atrophy, and sensorineural deafness). It is a slowly progressive neurodegenerative process, and there is also selective destruction of the pancreatic beta cells. Diabetes mellitus

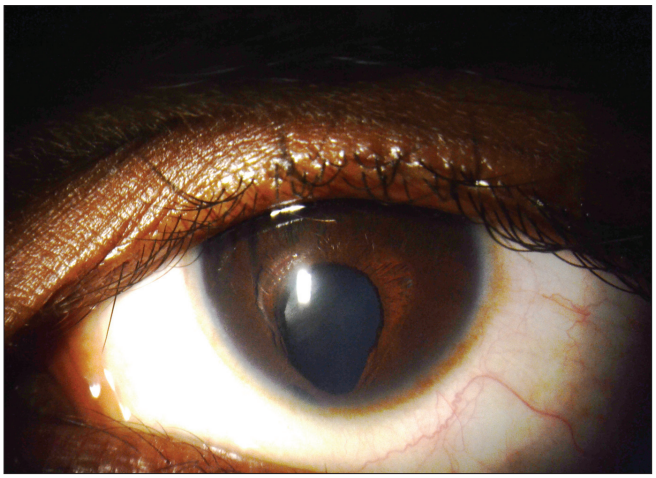

Figure 6a: Iris coloboma

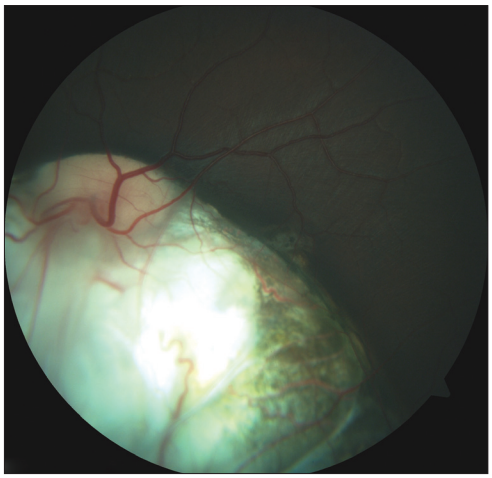

Figure 6b: Choroidal coloboma

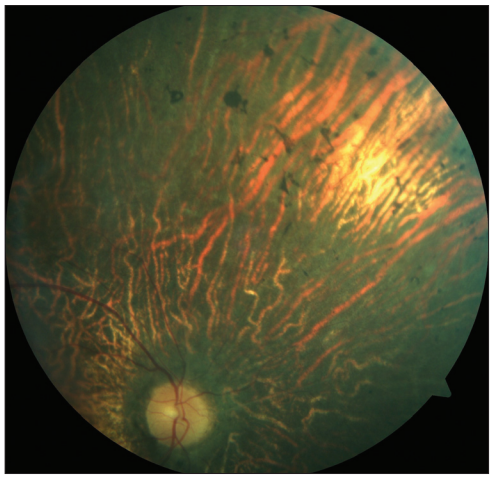

Figure 7: Retinal pigmentary degeneration

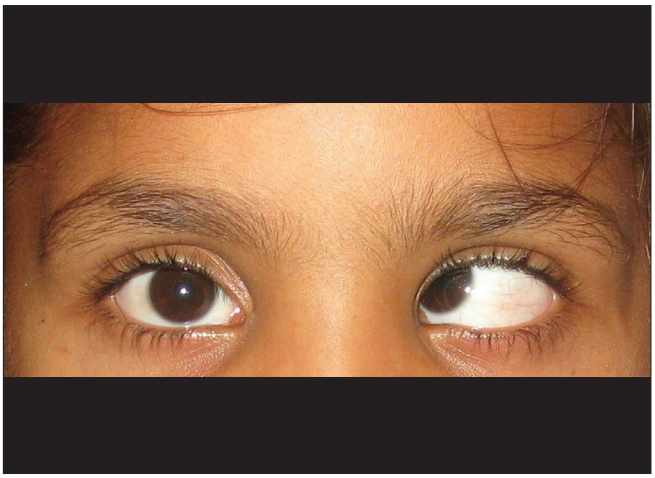

Figure 8: Child with strabismus

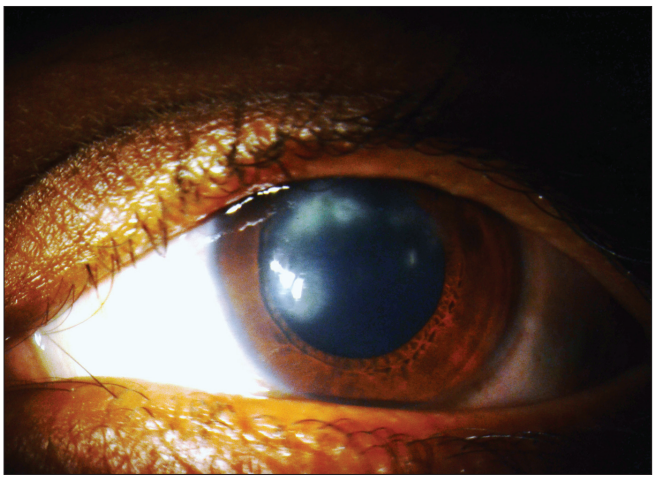

Figure 9: Chronic keratitis

with onset in childhood is often the first manifestation. Additional endocrinological abnormalities such as ACTH deficiency and growth hormone deficiency have also been reported.[56]

Ocular manifestations: ocular findings in Wolfram syndrome include a progressive bilateral optic atrophy. Hilson *et al*., in their report of the post mortem neuropathologic findings of a patient with Wolfram syndrome demonstrated a moderate to marked loss of retinal ganglion neurons and a loss of myelinated axons in the optic nerve.[57]

5. *Prader Willi syndrome:* Prader Willi syndrome is a relatively common and generally sporadic disorder with a recognizable pattern of dysmorphic features and major neurologic, cognitive, endocrine, and behavioral/psychiatric disturbances.[58] The major manifestations of this syndrome include hypotonia with poor suck and poor weight gain in infancy, mild mental retardation, hypogonadism, growth hormone insufficiency causing short stature, and early onset hyperphagia with obesity.[58]

   Ocular manifestations: patients with Prader Willi syndrome

are likely to have visual acuity disturbances and strabismus [Figure 8]. Myopia is the common refractive error seen in these patients.[59]

6. *Autoimmune polyendocrine syndrome I (APS-I):* autoimmune polyendocrine syndrome type I is a rare monogenic autosomal recessive disease characterized by a triad of major components hypoparathyroidism, adrenocortical insufficiency, and chronic mucocutaneous candidiasis. However, many lesser known minor components also occur as the natural history of the disease is highly variable. In the largest reported series of 91 Finnish patients, some patients suffered from minor manifestations of the disease for decades before the classical diagnostic criterion (presence of at least two of the triad) is fulfilled.[60]

   Ocular manifestations: chronic keratitis [Figure 9], dry eye, cataract, iridocyclitis, retinal detachment, and optic atrophy have been reported in APS-I.[61] Keratitis appears in 20–25% patients.[61] It is an early and sometimes the first manifestation of the disease. The etiology is probably an autoimmune attack on the corneal epithelium.

Clinical Approach to a Patient with Ocular Manifestations Suggestive of an Endocrine Disorder

Some of the common ocular presentations where an endocrine abnormality should be considered include optic atrophy wherein disorders such as Septo optic dysplasia (hypopituitarism and growth hormone deficiency), Kallman's syndrome (anosmia), and Wolfram's syndrome (diabetes insipidus) should be ruled out.

Visual field defects like bitemporal hemianopia usually result to due compression at the optic chiasma. In such conditions a brain magnetic resonance imaging should be performed to look for any pituitary lesion or empty sella syndrome as well as any fibrous dysplasia as seen in McCune Albright syndrome.

In patients presenting with decreased vision due to chorioretinal degenerations or dystrophies endocrine disorders such as Bardet Biedl syndrome, Kearns Sayre syndrome and Cockayne's syndrome should be considered. Primary hyperparathyroidism should be investigated for in a patient diagnosed with scleritis. Endocrine disorders such as Werner's and Rothmund's syndrome should be ruled in young patients with bilateral cataract. Lastly, in patients with chronic keratitis autoimmune Polyendocrine syndrome must be considered.

Conclusion

This review highlights the various uncommon endocrine disorders where ocular manifestations are significant. Problems in the eye may be a first presentation of the systemic disease or patients with known systemic problems may need to have their eyes specifically checked for complications. Knowledge of the ocular findings of endocrine disorders will help an endocrinologist reach a diagnosis, whereas the same knowledge will alert an ophthalmologist to seek the opinion of an endocrinologist when encountered with such findings. Awareness of these associations is the first step in the diagnosis and management of these complex patients.

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