

Ocular Manifestations of Endocrine Diseases

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Abstract

The human eye is an organ that can provide physicians with valuable clues for the recognition and management of many systemic diseases, including many disorders of the endocrine system. Ocular manifestations are common in many endocrine disorders such as diabetes mellitus and Graves' disease. However, there are a significant number of lesser-known endocrine diseases in which ocular changes are common. Endocrine glands communicate with each other through hormones. Hormones include cortisol, thyroid hormones, insulin, testosterone, estrogen and many others. They are made and stored in the endocrine glands and released by these glands to exert their effects on nearby or distant target organs. The main glands of the endocrine system are the hypothalamus, pituitary gland, adrenal glands, gonads (testes and ovaries), thyroid gland, parathyroid glands, and pancreas. Endocrine glands control the physiology of the human body and maintain its homeostasis. The effects of hyper or hyposecretion of each endocrine gland separately, usually manifest themselves in a multi-organ fashion. Some disorders of the endocrine system manifest in the eye first through a variety of distinct pathophysiological factors. It is an interdisciplinary pathology, falling under both endocrinology and ophthalmology, and knowing these ophthalmic manifestations is the most important step for the early detection, prevention, diagnosis, treatment and monitoring of these manifestations, which can thus significantly reduce the morbidity related to these disorders including permanent visual dysfunction.

Keywords: Ocular manifestations, Endocrine diseases, Endocrine ophthalmopathies.

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I. INTRODUCTION

The human eye is an organ that can provide physicians with valuable clues for the recognition and management of many systemic diseases, including many disorders of the endocrine system [1]. Ocular manifestations are common in many endocrine disorders such as diabetes mellitus and Graves' disease. However, there are a significant number of lesser-known endocrine diseases in which ocular changes are common [2].

The different parts and organs of the body must communicate with each other to function properly. Two systems contribute to this communication: the nervous system and the hormonal system also called neuroendocrine system (ensuring communication through the endocrine glands). Responsible for hormones secretion, the endocrine system is made up of several endocrine glands that are located in different

parts of the human body. It is strictly linked to the central nervous system, as it diversifies its functions through the hypothalamus and pituitary gland [3]. Endocrine glands communicate with each other through hormones. Hormones include cortisol, thyroid hormones, insulin, testosterone, estrogen and many others. They are made and stored in the endocrine glands and released by these glands to exert their effects on nearby or distant target organs. The main glands of the endocrine system are the hypothalamus, pituitary gland, adrenal glands, gonads (testes and ovaries), thyroid gland, parathyroid glands, and pancreas. Endocrine glands control the physiology of the human body and maintain its homeostasis. They are sometimes called ductless glands because they secrete their products directly into the blood or interstitial space [4].

The effects of hyper or hyposecretion of each endocrine gland separately, usually manifest themselves

in a multi-organ fashion. Some disorders of the endocrine system manifest in the eye first through a variety of distinct pathophysiological factors. Knowing these ophthalmic manifestations is the most important step for the early detection, prevention, diagnosis, treatment and monitoring of these manifestations, which can thus significantly reduce the morbidity related to these disorders including permanent visual dysfunction. Nowadays, the number of patients with endocrine ophthalmopathy is increasing, for various reasons related to environmental deterioration, consequences of man-made disasters, iodine deficiency, and heredity. Endocrine ophthalmopathies are due to pronounced functional changes of the eye, resulting in disability. It is an interdisciplinary pathology, falling under both endocrinology and ophthalmology [1].

The aim of this review is therefore to present the various ocular clinical signs occurring in the event of endocrine disorders based on published literature.

II. Ocular manifestations of endocrine disorders

2.1. Disorders of Thyroid gland

The thyroid gland is an endocrine gland, it consists of two interconnected lobes and located at the front of the neck region, below the laryngeal prominence. It secretes thyroid hormones thyroxine (T4) and triiodothyronine (T3), which influence metabolic rate, protein synthesis, and many other effects, including on development. Thyroid hormones T3 and T4 are synthesized from iodine and tyrosine and control strictly the use of energy by the body's cells through a process called metabolism. It is the main regulator of metabolism and affects all bodily functions. The thyroid also produces calcitonin, which plays a role in calcium homeostasis. Thyroid hormone production is regulated by thyroid stimulating hormone (TSH) secreted by the anterior pituitary gland, which in turn is regulated by thyrotropin-releasing hormone (TRH) secreted by the hypothalamus [5-7].

The ocular changes associated with thyroid dysfunction have been recognized for more than 150 years, yet controversy still remains regarding the pathogenesis, pathophysiology, and management of this disease [8]. Thyroid eye disease (TED) is associated with hyperthyroidism in 90% of cases, about 3% may occur in the setting of hypothyroidism and more than 10% of well-treated patients who are clinically in euthyroidism may still have orbital signs and symptoms [9-12]. Thyroid eye disorder remains the most known extrathyroidal manifestation of Graves' disease, and the most common cause of orbital and periorbital inflammation in adults. Patients with Graves' ophthalmopathy present significant ocular symptoms, which are consequences of increased hyaluronan production by orbital fibroblasts after activation by inflammatory cytokines and thyroid-stimulating immunoglobulins. This subsequent deposition of

hyaluronan in turn leads to expansion and pathologic changes in various ocular tissues, including orbital fat and extraocular muscles. [13-15] The severity of ophthalmic disease is not related to serum thyroid-stimulating immunoglobulin levels or serum thyroid hormone concentrations. The signs may be uni or bilateral. The major signs involved in Graves' ophthalmopathy are [13, 16-24]:

- **Eye lid retraction:** is one of the earliest and frequent signs causing exposure of superior sclera and widening of the palpebral fissure. It can be associated or not with other ocular signs.
- **Foreign body sensation:** can be related to various causes, including eyelid retraction that can cause corneal lubrication problems, and secondary and upper corneal keratitis or thickening of the conjunctival folds can prevent tear drainage and conjunctival hyperemia
- **Exophthalmia:** used to describe the proptosis of Graves' ophthalmopathy, can also cause problems of cosmetic nature being often asymmetrical;
- **Retraction of the upper eyelid:** is attributed to increased adrenergic activity of smooth muscle in the eye and is also caused by the inflammation that develops with fibrosis in the elevating muscle of upper eyelid. When exophthalmia is not severe, appear the signs and symptoms of foreign body sensation, chemosis and can be complicated by exposure keratopathy and corneal ulceration;
- **Restriction of ocular motility and diplopia:** are the consequences of infiltration of the extraocular muscles. Diplopia and decreased visual acuity are the main visual symptoms, these symptoms are aggravated in the morning when waking up, due to fatigue or alcohol consumption. Poor ocular motility is caused by the extraocular muscle's inflammatory congestion, lower right and right medial frequently, damage being initially reversible and through fibrosis processes becoming irreversible and by affecting the lower right it may be associated with elevated intraocular pressure;
- **Optic nerve dysfunction:** Optic nerve compression is one of the most serious complications of thyroid associated ophthalmopathy and it leads to decreased visual acuity. Its prevalence has been reported in approximately 10% of cases higher risk found in elderly males, it is manifested by decreased visual acuity, afferent pupil defect, loss of color vision or blurred disc borders. Corneal exposure and the appearance of its ulcers also contribute to decreased visual acuity;
- **Other ocular signs:** linked to Graves' disease are eyelid swelling, keratoconjunctivitis sicca and superior limbal keratoconjunctivitis.

Hypothyroidism does not usually cause eye disease, but metabolic consequences such as (hyperlipidemia, hyperlipoproteinemia) or neurological dysfunction usually cause potential ocular

complications. The most known metabolic consequences of hypothyroidism are corneal lipid deposits, corneal lipid deposits, lipemia retinalis, lipemic aqueous humor and its associated uveitis. Arcus lipoides corneae is most common in hypothyroid. The most known neurological dysfunction consequences are [25, 26]:

- **Horner's syndrome:** which is characterized by miosis, ptosis, enophthalmos and protrusion of the third eyelid;
- **Facial nerve palsy:** can cause corneal exposure resulting in keratitis or aggravating existing keratitis;
- **Keratoconjunctivitis Sicca (KCS):** which is characterized by dry eyes, can also cause secondary keratitis by exposure of the cornea. The simultaneous presence of hypothyroidism and KCS, could be attributed to an immune mediated process affecting the thyroid and lacrimal glands.

2.2. Disorders of Pancreas

Diabetes mellitus is the most common pancreatic disease resulting in significant ocular complications. It is a multi-systemic disease characterized by chronic hyperglycemia and other related metabolic disturbances such as dysregulation of carbohydrate, lipid, and protein metabolism. It is a global epidemic and the prevalence is anticipated to continue to increase. When diabetes is poorly managed, it can be responsible in the long term for severe and disabling micro and macrovascular complications. The most common microvascular complications remain nephropathy and retinopathy. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and the leading cause of blindness in working-age adults in developed countries. These ocular complications are secondary to an increase in vascular permeability and ischemia [27-29].

Ocular complications associated with diabetes:

- **Diabetic Retinopathy (DR):** DR affects more than 4.2 million people worldwide, making it one of the major causes of blindness. It can be divided into non-proliferative DR (NPDR) and proliferative DR (PDR), and diabetic macular edema (DME) [30, 31];
- **Cataract:** Cataract is one of the common causes of visual impairment in diabetic patients. A study conducted by Klein reported that more than 59% of people with type 2 diabetes between the ages of 30 and 75 will develop cataracts [32, 33];
- **Conjunctivitis:** Conjunctival bacterial infections, in particular acute infectious conjunctivitis are most commonly encountered in diabetics in about 86% of cases. These patients experience a significant increase in squamous metaplasia and a decrease in goblet cell density [34-37];
- **Corneal damage:** Ocular manifestations of diabetes also affect the cornea. Although

keratopathy is the best-known ocular complication of diabetes, several other corneal complications may occur during the course of diabetes namely, recurrent corneal erosions, persistent epithelial defects and corneal endothelial damage and laser in situ keratomileusis (LASIK) [38-41]

- **Neuropathy:** decreased retinal perfusion and microaneurysms may decrease the supply of oxygen to the optic nerve. This reduction in the supply of oxygen to the optic nerve for too long, can lead to apoptosis and induce permanent vision loss. Diabetes can also cause stress on the retina ganglion cells (RGCs) that triggers RGCs apoptosis [42-44];
- **Glaucoma:** The World Health Organization has classified glaucoma as a priority eye disease. Its prevalence is estimated at 79.6 million people in 2020. It is secondary to a failure to flow the aqueous humor through the trabecular mesh and Schlemm's canal, resulting in high pressure inside the eye. Increased pressure can damage nerves and blood vessels, leading to changes in vision, leading to glaucoma [45, 46];
- **Iris damage:** Neovascularization, secondary to the fall of capillaries in the retina, is the most serious consequence of diabetes on the iris and affects about 7 to 60% of diabetic patients. It is most often localized at the edge of the pupil, but at an advanced stage this neovascularization may extend to the entire surface of the iris and may be complicated by a peripheral anterior synechia or an ectropion uveae [47];
- **Dry eye:** Diabetic patients are at risk of developing tear film abnormalities and an increased incidence of dry eye. These pathologies may be secondary to a decrease in tear break-up time, which is an indicator of tear film stability. This decrease in tear break-up time is often due to either a peripheral neuropathy or a poorly controlled disease [37, 48];
- **Uveitis:** Studies had shown a correlation between type 1 diabetes and idiopathic anterior uveitis [37, 49].

2.3. Ocular manifestations in pituitary disorders:

The pituitary gland is developed from the diencephalon of the primitive brain. The diencephalon also gives rise to the posterior structures of the brain including the thalamus, hypothalamus, and pineal gland. The optic nerve is attached to the diencephalon and the retina is derived from the optic section, which is itself derived from the diencephalon [50]. The pretectal area derived from the diencephalon controls pupillary and behavioral responses to changes in light. The majority of the circadian rhythms of the organism are controlled by the regulated release of hormones. Melanopsin of retinal ganglion cells could activate the neuroendocrine system, which causes a change in the secretion of the hormone melanocyte-stimulating [51]. Hypothalamic-pituitary derived proopiomelanocortin

mediates the ultraviolet radiation-induced stimulation of the Langerhans cells in the retina [52]. A peptide with several functions isolated from the pituitary and hypothalamus named pituitary adenylate cyclase-activating polypeptide (PACAP) has been closely conserved over the last 700 million years of evolution. PACAP is found in neurological tissues, in the eye, ophthalmic artery and other structures, and also has an important role in regulating blood supply to the underlying tissues [53].

The ocular manifestations associated with pituitary disorders are caused by the immediate proximity of the pituitary gland to the optic chiasma in the upper region and the 3rd, 4th, and 5th nerves involved in the motility of the eyeball. Visual symptoms secondary to pituitary pathology are caused by the pressure exerted by the pituitary mass on the optic nerve, optic chiasm, or tract [1]. They remain the major signs of non-functioning pituitary and gonadotrophic adenomas, although their prevalence is decreasing, due to earlier screening during intracranial imaging performed for other indications [54, 55].

A symmetrical narrowing of the visual field called bitemporal hemianopsias may be linked to a growing pituitary tumor. The visual symptoms seen in pituitary tumors vary with the size of the tumor. Microadenomas (less than 1 cm in diameter) usually give no ocular symptoms. Initially, the damage caused by compression is limited to the lower fibers of the optic nerves that carry visual information from the superior and temporal fields resulting in early loss of the supra-temporal quadrants and as compression continues, it damages the upper fibers of the optic nerve on both sides of the optic chiasm, leading to complete bitemporal hemianopia. Incongruous homonymous hemianopsia can be observed in patients with a prefixed chiasma, but a decrease in visual acuity, a decrease in color vision or a contralateral junctional scotoma are most often encountered in those with a postfixed chiasma, in case of optic chiasma compression. Compression of the optic chiasm from above is characterized by inferotemporal quadrantanopia often encountered in craniopharyngiomas. The presence of visual symptoms in pituitary microadenomas should prompt the clinician to seek an alternative etiology. Apart visual signs which might be due to increased intracranial pressure, compression of structures in the visual pathway, and involvement of cranial nerves in the cavernous sinus, others signs, namely, alterations in body weight, stature, growth rate and progression of puberty, can help to make the diagnosis of pituitary disorder. Overlooking these subtle manifestations might also contribute to the delay in the diagnosis of the underlying endocrine disorder [1, 52, 56].

2.4. Ocular manifestations in Parathyroid disorders

The parathyroid gland secretes parathyroid hormone (PTH), a polypeptide, in response to low calcium levels detected in the blood. PTH facilitates the synthesis of active vitamin D, calcitriol (1,25-dihydroxy vitamin D) in the kidneys. In conjunction with calcitriol, PTH regulates calcium and phosphate. PTH effects are present in the bones, kidneys, and small intestines. As serum calcium levels drop, secretion of PTH by the parathyroid gland increases [57].

Ocular manifestations related to hypercalcemia include calcification of the conjunctiva, eyelids, or cornea (keratopathy of the band). In the case of hypocalcemia, the lens develops multiple pint-shaped opacities usually located in the sub-capsular region which, by progression, involves the lenticular cortex. An imbalance in the active cation transport mechanism could lead to osmotic imbalance and subsequent fiber breakage and cataract formation. Treatment with vitamin D and calcium supplements can stop the progression of cataract formation [58-60].

2.5 Ocular manifestations in Adrenal gland disorders

➤ Addison's disease:

Addison's disease or primary hypoadrenalism is secondary to a deficiency in the secretion of glucocorticoid and mineralocorticoid hormones by the adrenal cortex. It is associated with:

- Idiopathic, surgical or infectious destruction;
- Infiltration of the cortex by sarcoidosis, tuberculosis, or amyloidosis;
- A tumor of the parenchyma of the adrenal gland [3].

Ocular pathologies are rare in Addison's disease, nevertheless, ptosis, blepharitis, Blepharospasm, keratoconjunctivitis with extreme photophobia, corneal ulcers, episcleritis, cataract, and papilloedema are often encountered [61].

➤ Cushing's syndrome:

Cushing's syndrome (CS) was first described by Harvey W. Cushing in 1932. He reported 12 patients with a severe metabolic disorder, which he attributed to pituitary basophilic tumors. At present, the term Cushing's syndrome refers to the clinical symptoms and signs of prolonged exposure to inappropriately elevated levels of free plasma glucocorticoids. The endogenous causes of Cushing's syndrome are rare and result in loss of the normal feedback mechanism of the hypothalamic-pituitary axis and normal circadian rhythm of secretion of cortisol [62].

Increased intraocular pressure and exophthalmos associated with increased retro-orbital fat deposition, are the ocular manifestations most frequently encountered in Cushing's disease. Cataracts

occur as a complication of long-term corticosteroid therapy [2, 63].

III. CONCLUSIONS

We found through this study that close collaboration between endocrinologist and ophthalmologist remains essential for complete management of ocular manifestations of endocrine diseases, because eye and its adnexa can be involved in several different ways in endocrine disorders and the ocular manifestations vary. Many ophthalmic conditions are secondary to endocrine and hormonal imbalances. It is important to diagnose the primary cause of ocular changes in patients early and to consider the eventual presence of endocrinopathies. Early initiation of therapy is an important factor in stopping the development of the disease and the increasing risk of persistent ocular changes, including vision impairment. To this effect, a team-based approach to care for these patients is one model that can facilitate cross-communication, education, and provide a convenient framework for clinic visits.

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