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OPHTHALMOLOGY MANIFESTATION OF ENDOCRINE DISORDERS, ENDOCRINOLOGY, AND THE EYE.

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Abstract:
Disorders of the endocrine system have usually multi-organ manifestations. It might be a disorder of one specific organ/ gland, for the instance thyroid gland, but it will be diagnosable through an examination of other organs like eyes. Specifically, endocrinopathies through distinct pathophysiological issues, become apparent in the eyes first. Eyes provide a gateway to physicians for the recognition and treatment of various systemic diseases. The ophthalmic manifestation of endocrine disorders is extremely important to prevent significant mortality and morbidity rates by on-time diagnosis and treatment.
In this research paper, ophthalmic related findings linked to prominent disorders of the thyroid gland, pancreas, and hypothalamic-pituitary axis are discussed. Grave's ophthalmopathy, diabetes mellitus, and pituitary tumors are discussed below, respectively, that will throw light on the unique relationship of these endocrine disorders with the eye.

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INTRODUCTION:

Disorders of the endocrine system have usually multi-organ manifestations. It might be a disorder of one specific organ/ gland, for the instance thyroid gland, but it will be diagnosable through an examination of other organs like eyes. Specifically, endocrinopathies through distinct pathophysiological issues, become apparent in the eyes first. Eyes provide a gateway to physicians for the recognition and treatment of various systemic diseases. The ophthalmic manifestation of endocrine disorders is extremely important to prevent significant mortality and morbidity rates by on-time diagnosis and treatment.

In this research paper, ophthalmic related findings linked to prominent disorders of the thyroid gland, pancreas, and hypothalamic-pituitary axis are discussed. Grave's ophthalmopathy, diabetes mellitus, and pituitary tumors are discussed below, respectively, that will throw light on the unique relationship of these endocrine disorders with the eye.

Disorder of the Thyroid Gland

- **Grave's Disease**

The most common cause of hyperthyroidism around the world is Grave's disease with 19- 49 cases per 100,000 individuals per annum. [1] This disorder typically appears in the third or fourth decade of life and is more inclined towards females. As it has usually autoimmune conditions, so Grave's disorder is linked with some human leukocyte antigens (HLA), including HLA Bw35 specifically in Asians.

Symptoms:

Symptoms of hyperthyroidism include fatigue, anxiety, and heat intolerance. Specifically, Grave's disorder often includes weight loss, tremor, sweating, pretibial myxedema, digital clubbing and many CVD changes like bounding peripheral pulses, arrhythmias, and tachycardia. [2]

Similarly, the eye and orbit of the patient with Grave's disorder show a variety of symptoms and signs that encompass the ophthalmic elements. 90% ratio of patients with grave's disease is hyperthyroid, others can be hypo or euthyroid. [3]

Pathophysiology of Ophthalmic Demonstration

In Grave's disease IgG autoantibodies are activated that participates in evasion of immune system regulation. These antibodies affect thyroid hormone production by targeting thyrotropin receptors. [1] Grave's ophthalmopathy ascribes activation of inflammatory cytokines and thyroid-stimulating immunoglobulins that impacts orbital fibroblasts which in turn increases the hyaluronan production. The rise in hyaluronan production leaves pathological impacts upon various ocular tissues including orbital fat and extraocular muscled. [3] As no direct link was found between the levels of serum thyroid hormone and thyroid-stimulating immunoglobulin concentrations in patients, thus thyroid alone cannot aid in the diagnosis of Grave's disease. It can also not tell about the severity of ophthalmic disease all alone.

Clinical Presentation

In Grave's disease, the most common systematic manifestation is a thyroid eye disease which is visible in 50% of these patients. [5] Eyelid swelling, wide-eye stare, and symptomatic diplopia are early visible symptoms. Grave's ophthalmopathy can be confirmed with the appearance of factors like strabismus, eyelid retraction, exophthalmos, optic nerve dysfunction, and restricted extraocular mobility.

Table: prominent ophthalmic symptoms of thyroid eye in the diagnosis of Grave's ophthalmopathy [7]

Symptoms	Incidence (%)
Eyelid retraction	
Eye pain	30
Optic nerve dysfunction	6
Exophthalmos	62
Restricted extraocular motility	43
Diplopia	17
Tearing	21
Photophobia	16
Blurred vision	8

Proptosis of Grave's ophthalmopathy is also described as exophthalmos, it can make patients prone to corneal ulceration and keratopathy. [3] Examination of extraocular muscle infiltration has shown restricted ocular motility and diplopia in patients. The medial and inferior recti muscles are the earliest affected ones. Loss of color vision, decreased visual acuity, afferent pupillary defect, blurred disc margins, conjunctival chemosis, eyelid swelling, keratoconjunctivitis sicca, superior limbic keratoconjunctivitis are the prominent features included in Grave's ophthalmopathy detected upon fundoscopic examination. [1] In severe conditions, the patient might well have permanent changes in the function and appearance of ocular eye structures.

Treatment

Treatment and management of Grave's disease are complicated and multi-faceted. Radioactive iodine ablation therapy, anti-thyroid drugs, and thyroid surgery are the well-known options implemented either individually or in combination with one another. Oral steroids or external beam of orbital

radiation is also directed in some cases. Cigarette smoking is strictly ceased to prevent disease enhancement. 50% of patients administered with ATDs show recurrence of the disease and radioactive iodine therapy treatment has been proved promising here. But, studies have shown that in 15% of patients it can cause progression of ophthalmopathy. Lastly, surgery is the fine option for patients with large goiter who prefer surgical to medical therapy.

Treatment for ophthalmopathy usually depends upon the severity of the disease. Ophthalmologists mostly recommend intensive ocular lubrication to protect against exposure keratopathy due to dysfunctional eyelid which can cause corneal decompensation. Additionally, photophobia can be controlled with the use of sunglasses, and periorbital edema can be reduced by elevating the head of the bed at night. However, ophthalmic complications may require surgical intervention, and among them, orbital decompression is the most critical one which is performed on patients with the threat of vision loss and compressive optic neuropathy.

Disorder of the Pancrease

- **Diabetes Mellitus (DM)**

In 2014, the estimated DM global prevalence was 423 million, and according to Centres for Disease Control and Prevention the projection was expected to rise by 2050, one in three adults may have it. [8, 9] Patients are at higher risk for both macro and microvascular diseases with DM, particularly coronary artery, stroke, peripheral arterial disease, nephropathy, retinopathy, and neuropathy. Diabetes is the leading cause of blindness in people under the age of 75.

Diabetic retinopathy has significant value in the determination of CVD and mortality in diabetic patients. [10]

Pathophysiology of Ophthalmic Demonstration

A wide range of ophthalmic complications is associated with diabetic eye diseases including retinal pathology like DR, macular edema, poor corneal healing, cataracts, anterior segment pathology, and ophthalmic vascular disease.

Hyperglycemia takes part in retinal injury through sorbital and glycosylation end products' accumulation in retinal endothelial cells and impaired retinal blood flow. Impaired endothelial cell functions lead to various complications like enhanced vascular endothelial growth factor, abnormal retinal vascularization, and accumulation of extracellular fluid in the retinal tissues. [11, 12]

DR has two entities, proliferative (PDR) and no proliferative (NPDR). In the early stage of the later entity, hyperglycemia occurs which is clinically detected as cotton wool spots and small spots of intraretinal blood upon examination. In the deep layers of the retina, intraretinal hemorrhage can occur due to the rupture of weak walls of capillaries, also known as microaneurysm. With the progression of the disease, retinal blood barrier can breakdown that will lead to serum protein and lipids leakage into the retina. These changes are observed in the form of yellow-white deposits along the border of retina edema. The progression of NPDR to PDR is observable after the inadequate oxygenation of the retina that releases abnormal growth factors like insulin (IGF-1) and VEGF, to re-vascularize the diseased area. The development of new blood vessels becomes a threat to the vision, which was formed to fight retinal ischemia. These abnormal, feeble vessels can become a cause of leakage into retina, vitreous, trabecular meshwork, and to many associated regions.

The abnormal blood vessel formation in anomalous regions can cause blinding complexity like neovascular glaucoma which can cause permanent damage to the optic nerve, and fibrovascular tissue formation that can detach the tractional retina. [13, 14] When excessive vascular permeability occurs in the macula it can cause visual morbidity if not treated on time. Venous thrombosis is another drastic effect of DM, it can also lead to loss of vision but it entirely depends upon the associated macular edema and degree of residual retinal perfusion. [14]

Clinical Presentation

In both types of DM, either it is type 1 DM or type 2 DM, DR is potentially a blinding complication in these patients with 90% and 60% ratio, respectively. [15] Complaints like loss of parts of the visual field, declined visual acuity, floaters and new-onset flashes, and bilateral movement in patients might be recorded. [16, 17] In 3 years time frame, patients are at moderate risk of losing their vision by 20- 30% who have clinically significant macular edema (CSME).

Cataracts are observed at a very young age (12) in individuals with diabetes. These patients tend to notice face increase glare, blurry field of vision, halos around lights, deficits at night, and distorted, bent, or wavy structure of vertical lines. [11] Patients encounter the paralysis of the sixth cranial nerve up to one-half of all cranial nerves who have poorly handled diabetes. Inversion of the lateral rectus muscle is linked with this eye, so esotropia and binocular diplopia results. [18]

Early and regular ophthalmic examination is extremely important to predict the onset of ocular symptoms.

Treatment

Studies from the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control

and Complications Trial (DCCT) showed that to control ocular manifestation associated with DM, it is important to have glycemic control. It is found that intensive or conventional insulin therapy decreased the incidence of DR by 50%, its progression by 50%, and the risk of peripheral neuropathy by 60%. Conventional and intensive glucose control with T2DM showed a 25% decline in microvascular complications. In the medical management of DR, metabolic control, blood pressure control, glycemic control, and the efficacy of agents targeting the rennin angiotenin system along with PPAR- α, are quite helpful. [10]
Treatment of retinal disease via surgery, pan-retinal photocoagulation and intravitreal anti-VEGF agents, is usually carried out. Visual potential in patients can be maximized if these modalities are used appropriately. In patients with cataracts, cataract extraction with monocular lens placement is the best option, but patients with DM might face post-operative complications.

Disorder of the Hypothalmic- Pituitary Axis

- **Pituitary Tumors**

The pituitary fossa can be occupied by two types of tumors. One is Craniopharyngiomas, which accounts for up to 90% of pediatric tumors in the pituitary region. On the other hand, the second one is pituitary adenomas that comprise only 27% of supratentorial tumors in children. The later tumor is usually benign and is classified according to functional status, size, a hormone secreted (gonadotropin hormone, growth hormone, adrenocorticotropic hormone, and thyroid-stimulating hormone), and primary cell origin. [19]

In adults and children, prolactinomas are the most common pituitary adenomas, and 53% of pediatric pituitary adenomas are seen as prolactinomas. Through neurological manifestation and intracranial expansion, these masses are observable; over or under hormone secretion or distinct clinical symptoms can sometimes also aid in their detection. [20]

Pathophysiology of Ophthalmic Manifestations

The location of the pituitary gland is sella turcica which is also known as pituitary fossa. It is a saddled shape depression on the upper side of the sphenoid bone. Superior to the pituitary gland and anterior to pituitary stalk, optic chiasm is present that contains optic nerves and tracts. However, the location of optic chiasm may be anterior and posterior to the gland in 15% or 5% cases, respectively. Nasal fibers run in the medial direction of optic nerves and then across the chiasm, they decussate to the contralateral side of the optic tract. The temporal fibers of the retina lie on the ipsilateral side of the optic fibers and run laterally. On either side of the pituitary fossa, there lie the cavernous sinuses and each of them contains trochlear (IV), ipsilateral oculomotor (III), and abducen cranial nerves (VI), internal carotid artery and ophthalmic (V1) and maxillary branches (V2) of trigeminal cranial nerves.

All this anatomic configuration defines the ocular manifestations linked with pituitary disorders.

Clinical Presentation

Mechanical compression of the optic nerve, tract and chiasm leads to visual symptoms of pituitary mass. Abnormalities in the vision field detect the presence of tumors. When pituitary tumor enlargement and subsequent optic chiasm compression occurs, then it results in classic bitemporal hemianopsia. Initially, the inferior fibers of the optic nerves are damaged which causes loss of supratemporal quadrants. Continued compression leads to complete bitemporal hemianopsia due to damage of superior fibers of optic nerve present on both sides of the chiasm. [16]
A prefixed chiasm state, compression of the optic tract can lead to incongruous homonymous.

If defects in visual field progress without detection, the patient can face an insidious decline in vision, despite good visual acuity tests and it can leave physicians perplexed. Ultimately, when pituitary mass puts chronic depression on the nerve it can cause irreversible, diffuse atropy of the optic nerve which is associated with visual field loss. Partial or complete ophthalmoplegia, diplopia, ptosis, papillary anomalies, and facial pain can result when pituitary fossa laterally extends into cavernous sinuses and began to affect cranial nerves. Such conditions are features of rapidly and aggressively growing tumors associated with poor prognosis. [21]

Treatment

Surgical resection, radiation therapy, and medical management are well-known options to reduce the mass size and effects of pituitary tumors. In patients bearing pituitary adenomas with 20/100 visual acuity, post-operative improvements in ophthalmologic symptoms are observed. Although in some cases, bromocriptine, a dopamine agonist, has shown efficacy in size reduction of prolactinomas, these medical agents are less effective in the growth hormone-secreting adenomas and ACTH-secreting adenomas treatment. The size of the tumor defines the chances of reoccurrence. Treatment is usually carried out in a combination of surgical resection, radiation therapy, and/or cyst drainage.

CONCLUSION:

The study of the eye reveals various facts about the human body. When the body is ill, ophthalmology manifests various symptoms that are specifically

linked with many diseases. Specifically, endocrine disorders can be detected via ophthalmic examination. Careful and on-time detection of the disease can save the patient from developing complications. Therefore, it is important to have regular yearly check-ups, and physicians must keep track of their patient's medical history for appropriate diagnosis and treatment.

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