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Pituitary Adenomas and Ophthalmology

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1. Introduction

Pituitary gland, also called hypophysis, is a neuroendocrine organ placed in the "sella turcica" in the skull base. This gland consists of 2 main areas, the anterior and medial part constitute the adenohypophysis, the posterior part is called neurohypophysis. Pituitary gland is in charge of the internal constancy, homeostasis and reproductive function; this is why pituitary abnormalities cause a wide spectrum of signs and symptoms.

Pituitary adenomas are a common pathology; they represent about 10% of all intracranial tumours and between 50-80% of pituitary tumours. Necropsy and imaging studies estimate an incident of 20-25% of pituitary adenomas in general population; however, only about 1/3 of them are clinically evident (Asa & Ezzat, 2009). The majority of these tumours have monoclonal origin (mutation of a single gonadotropic cell), but there are still some discrepancies about the pathogenesis of these neoplasms. The most common mutations seem in other human neoplasms are not frequent in pituitary adenomas, and only a minimum proportion of them are associated to other genetic disorders, such as MEN1 syndrome (multiple endocrine neoplasms type 1) or the Carney complex, due to mutations of the genes MEN1 and PRKAR1A (protein kinase A regulatory subunit 1A) respectively (Beckers & Daly, 2007). Hormones and growth factors involve in normal pituitary function can be also related to the growth of these tumours, although evident connection with the pathogenesis has not been demonstrated.

Symptoms related to pituitary tumours are secondary to several factors. On the one hand, many of them are *non-secreting tumours*, they can be asymptomatic or cause compression symptoms if they are big enough; on the other hand, other are *secreting tumours* and they can cause clinical syndromes derivate from the hormone activity in different target organs. Hormones secreting by these tumours are the same that the physiologic hypophysis produces. According to frequency, the most frequent tumours are prolactin (PRL)-secreting pituitary adenomas, non secreting pituitary adenomas are in second position, growth hormone (GH)-secreting tumours in third, adrenocorticotropic hormone (ACTH)-secreting tumours in fourth, and the rarest are thyroid stimulating hormone (TSH)-secreting adenomas. There are also tumour secreting different combinations of hormones, mainly GH and PRL (Table 1). In cases of fast growing or big tumours affecting surrounding structures, chiasmatic or cavernous sinus syndrome can be seen.

Two types of adenomas can be described depending on the size of the tumour, macroadenomas with more than 1 centimeter and microadenomas measuring less than 1 cm

in size (figure 1). A low percentage of tumours have a malign behaviour producing metastases, central nervous system invasion and even death; nevertheless, this is very uncommon and the majority of the problems related to these tumours are due to the morbidity that they produce.

Cell type	Hormones	Hormone function			
Adrenocorticotropic	ACTH and other peptides	Adrenal cortex; glucocorticoid metabolism	10 - 15%	Cushing syndrome Nelson syndrome	
Somatotropic	GH	IGF-1 production. Muscle and bone growth	10 - 15%	Acromegaly Gigantism	
Lactotropic	PRL	Lactation	35%	Amenorrhea Galactorrhea Sexual dysfunction	
Mammo- somatotropic	GH , PRL	See above	5%	Acromegaly Gigantism with hyper-PRL	
Thyrotropic	TSH	Thyroid metabolism	2%	Hypo - hyperthyroidism	
Gonadotropic	FSH, LH	Sexual development. Sexual steroids metabolism	35%	Hypogonadism Mass effect Hypopituitarism	

Table 1. Pituitary cells, hormones, tumours and associated clinical syndromes (Asa & Ezzat, 2002)

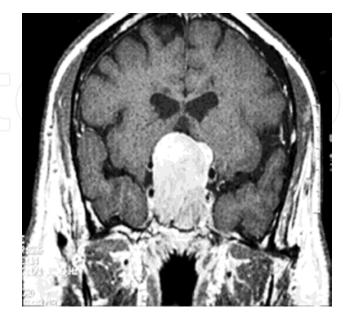


Fig. 1. Magnetic resonance imaging showing a pituitary macroadenoma.

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The wide spectrum of clinical syndromes including endocrinological, cardiovascular, neurological, ophthalmological, determine the needed of a multidisciplinary management between different specialists. Early diagnosis is very important in order to establish a proper therapeutic plan and achieve the best prognosis for these patients.

In this review, a comprehensive description about the ophthalmological syndromes associated to pituitary adenomas is presented. The suspicion of these syndromes by the doctors facing patients with pituitary tumours will allow earlier diagnostic and better treatments for them. Despite the general ophthalmic examination including visual field tests, we describe the Optical Coherence Tomography (OCT) as a new tool that must be performed in all these patients.

2. Ophthalmic manifestations of pituitary adenomas

The most common neuro-ophthalmological syndrome associated to pituitary adenomas is due to compression of the central part of the optic chiasm; this produces the classic bitemporal hemianopia in the visual field. That was the onset manifestation in up to 80% of pituitary adenomas several years ago, but nowadays, the advantages in the hormone detection tests and neuroimaging have changed this trend, and headache and systemic clinical syndromes related to hormone production are the commonest onset manifestations. Neuro-ophthalmological manifestations are the debut syndrome in less than 10% of cases (Table 2); they are due to the anatomical relations between the gland and the optic chiasm, the optic nerves and the III, IV and VI nerves in the cavernous sinus.

Study. No of patients Year	Amenorrhea/ Impotence(%)	Headache (%)	Visual dysfunction (%)	Optic atrophy (%)	EOM impairment
Chamblin et al (156;<1955)			86	50	5
Hollenhorst and younge (1000;1940-62)	5	14	70	34	6
Klauber et al (51; 1967-74)		45	69	47	
Wray (100; 1974-76)	21	24	31	19	4
Anderson et al (200; 1976-1981)	70	46	9	2	

EOM: extraocular muscle

Table 2. Debut signs and symptoms in pituitary adenoma patients (Chhabra & Newman, 2006)

2.1 Anatomy of the pituitary area (Rouvière & Delmas, 1996)

Optic nerves enter the intracranial space through the *optic foramen* in the sphenoid bones, after 8-15 mm up and backwards they join together to constitute the optic chiasm. There are anatomical variations in the length of the intracranial optic nerve and the position of the

optic chiasm, this is extremely important with respect to the visual deficits caused by tumours in the suprasellar region. In 75-80% of people optic chiasm is placed just above the *diaphragma sellae*; when the intracranial optic nerve is shorter than about 12 mm (about 10% of people), the optic chiasm is positioned anteriorly, or "pre-fixed", and it sits above the *tuberculum sellae*, when the intracranial optic nerve is long, over 18 mm (10-15% of people), the chiasm is positioned posteriorly to the *dorsum sellae* or "post-fixed" (Chhabra & Newman, 2006; Miller N, et al, 2008).

Fibers running from the nasal retinal nerve cells (about 53% of fibers) cross in the chiasm to join the fibers from the temporal retinal nerve cells of the opposite side. However, as they enter the chiasm, some ventral crossed fibers, primarily from the inferonasal retinal of the contralateral eye and serving the superotemporal portion of the contralateral visual field, where historically believed to loop anteriorly 1 to 2 mm into the terminal portion of the opposite optic nerve before turning posteriorly to continue through the chiasm and into the optic tract. This loop is called Willebrand's Knee (Miller N, et al, 2008; Muñoz-Negrete & Rebolleda, 2002). There is some controversy about the real anatomical existence of this structure, however Willebrand's knee clearly exists from a clinical point of view, as it is described below. In cases of chiasm compression the crossed fibers are more likely to be damaged as they support the same quantity of pressure in less space (Kosmorsky, et al, 2008). This is the reason for the bitemporal hemianopia (crossed nasal fibers compression) as the more frequent syndrome in cases of chiasm compression. Fibers leave the chiasm backwards in both sides of the hypophysis as the optic tracts; in cases of pre-fixed chiasms is more likely to see damaged of these tracts.

The pituitary gland lies between the two paired cavernous sinuses. An abnormally growing adenoma will expand in the direction of least resistance and eventually compress the cavernous sinus (figure 2). The cavernous sinus receives blood via the ophthalmic vein through the superior orbital fissure and from superficial cortical veins, and is connected to the basilar plexus of veins posteriorly. The internal carotid artery (carotid siphon), and cranial nerves III, IV, V₁, V₂ and VI all pass through this blood filled space. The cavernous sinus drains by two channels, the superior and inferior petrosal sinuses, ultimately into the internal jugular vein. These nerves, with the exception of V₂, pass through the cavernous sinus to enter the orbital apex through the superior orbital fissure. The maxillary nerve, division V₂ of the trigeminal nerve travels through the lower portion of the sinus and exits via the foramen rotundum (Miller N, et al, 2008; Frank, et al, 2006).

2.2 Clinical syndromes

There are different syndromes that can be seen in cases of pituitary adenomas:

2.2.1 Anterior chiasmal syndrome

This is more common in post-fixed chiasms. The compression in the anterior angle of the optic chiasm affect the *Willbrandt's knee* fibers and produces temporal and superior visual field defects affecting one or both eyes. In cases of non-centred tumours the anterior junction syndrome of Traquair (junctional scotoma) can be observed, characterized by advanced visual field loss affecting the visual field centre in one eye and (possibly subtle) defects respecting the vertical midline in the fellow eye (Muñoz-Negrete & Rebolleda, 2002).

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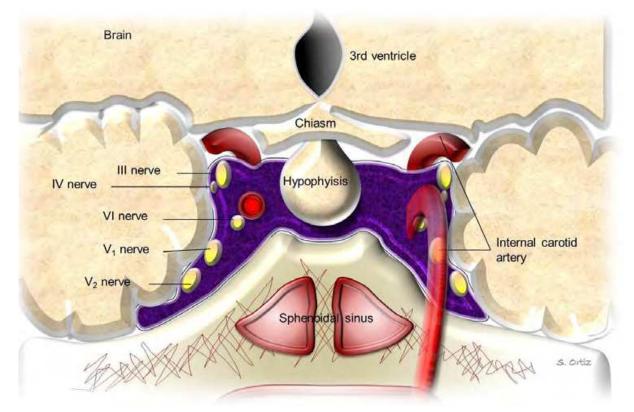
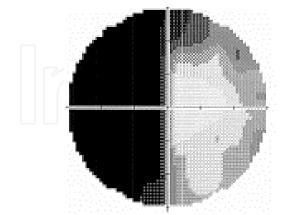


Fig. 2. Anatomy of the cavernous sinus and surrounding structures. Relation between the pituitary gland and the chiasm, cranial nerves and internal carotid arteries.

2.2.2 Central chiasmal syndrome

This is the most frequent syndrome; the damage involving mainly the crossed fibers produces bitemporal hemianopia with possible central visual field affectation (figure 3). This syndrome is seen in lesions that damage the body of the optic chiasm.



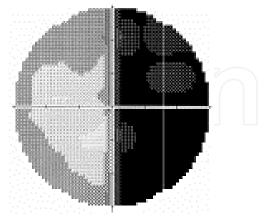


Fig. 3. Visual field showing a bitemporal hemianopia.

2.2.3 Inferior chiasmal syndrome

If the compression affects predominantly the inferior part of the chiasm the visual field defects are temporal and superior.

2.2.4 Superior chiasmal syndrome

Compression of the superior part of the chiasm is not a frequent condition in cases of pituitary adenomas; it is more likely to see this clinical picture in other tumours arising from the base of the brain, mainly the craniopharyngioma. In these cases the visual field defects are temporal and inferior.

2.2.5 Posterior chiasmal syndrome

More frequent in pre-fixed chiasms. It produces characteristic bitemporal hemianopic scotomas in the visual field.

2.2.6 Lateral chiasmal syndrome

This syndrome can be observed in tumours compressions or carotid pathology that pushes the chiasm laterally. Contralateral homonymus quadrantanopic or hemianopic defects can be assessed; much less frequent is the binasal hemianopia in these cases.

2.2.7 Optic tract compression

This is also more frequent in cases of post-fixed chiasms. Contralateral homonymus defects can be observed. Optic tract damage is more frequent in other neurological conditions, such as vascular processes, demyelinating diseases or trauma. Another pupillary phenomenon that is sometimes associated with lesions of the optic tract that produce a complete or nearly complete homonymus hemianopia is pupillary hemiakinesia (hemianopic pupillary reaction or Wernicke's pupil) (Miller N, et al, 2008).

2.2.8 Neuro-ophthalmological signs and symptoms associated with the chiasmal syndrome

The presence of visual field defect can associate different manifestations, such as the *hemifield slide phenomenon* that produces fluctuating diplopia with no oculomotor impairment due to anomalous retinal correspondence. It is also common a *disturbance of depth perception*. These two phenomenons are associated to bitemporal hemianopia (Chhabra & Newman, 2006; Miller N, et al, 2008).

2.2.9 Ocular motility disorders

Patients with pituitary pathology can refer diplopia related to the mentioned hemifield slide phenomenon, or due to cranial nerves damage in the cavernous sinus; the most frequently affected is the third nerve leading to an eyelid ptosis, pupillary dilation, and ocular motility disorders (figure 4). The rarest of those syndromes is the VI nerve palsy.

2.2.10 Nystagmus

In cases of tumours of the diencephalon and chiasmal regions the rare phenomenon of the "see-saw" nystagmus may occur. This condition is characterized by synchronous alternating elevation and incyclotorsion of one eye and depression and excyclotorsion of the opposite eye. The pathogenesis of this phenomenon is not well understood but it is thought to be related to perception impairment connected with hemianopia (Chhabra & Newman, 2006)



Fig. 4. Patient affected by a III nerve palsy. Observe the eyelid ptosis due to affectation of the levator muscle. These patients also have pupillary dilation and extraocular movements impairment

or damage to the interstitial nucleus of Cajal or adjacent structures of the tumour (Miller, et al, 2008). In cases of big tumours compressing the brainstem is also possible, although exceptional, the presence of nystagmus.

2.2.11 Colour vision impairment

This can be observed as a sign of visual pathway damage in different conditions, including cases of pituitary adenomas.

2.2.12 Photophobia

Some authors suggest that persistent photophobia of unknown aetiology should arise the suspicion of pituitary pathology (Kawasaki & Purvin, 2002).

2.2.13 Pituitary apoplexy

Defined as a sudden neurologic impairment, usually due to a vascular process. It is characterized by a sudden onset of headache, visual symptoms, altered mental status, and hormonal dysfunction due to acute hemorrhage or infarction of a pituitary gland. An existing pituitary adenoma is usually present. The incidence of this phenomenon has been described up to 10% in some series (Wakai, 1981). The visual symptoms may include both visual acuity impairment and visual field impairment from involvement of the optic nerve or chiasm and ocular motility dysfunction from involvement of the cranial nerves traversing the cavernous sinus (more frequent III nerve). Other less common symptoms are related to possible brainstem damage, such as light-near dissociation or convergence retraction nystagmus.

2.2.14 Funduscopy

Most of the cases show normal optic discs in fundus examination. If altered, it can be a diffuse atrophy, or more typically the "band" or "bow-tie" atrophy that occupies a more or less horizontal band across the disc with relative sparing of the superior and inferior portions where the majority of spared temporal fibers enter (figure 5). Some cases can develop papilledema, this is more frequently associated with suprachiasmal tumours that can invade and compress the 3rd ventricle, ultimately obstructing the flow of cerebrospinal fluid.

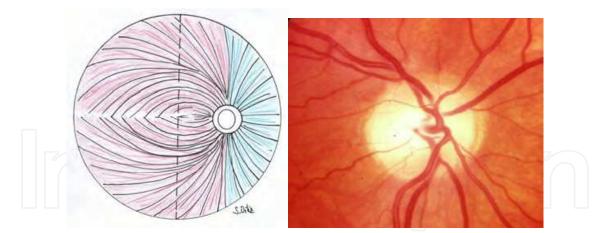


Fig. 5. Schematic representation of retinal nerve fibers (A). Optic disc of a patient with a pituitary adenoma showing atrophy of the nasal and temporal areas ("band" atrophy) and relative spare of the superior and inferior areas of the disc (B).

2.2.15 Other neuro-ophthalmological manifestations

Apart from the syndromes derivated from the tumour itself, the treatments used in these patients can produce neuro-ophthalmological side-effects:

- Toxic dopaminergic psychosis caused by *Bromocriptine*. Treatment with this drug can also produce a quick tumour regression leading to an *empty sella syndrome* due to a herniation of the chiasm.
- The surgical treatment most frequently performed today for these patients is the endoscopic trans-sphenoidal surgery. This technique can be also responsible for some ophthalmological side effects, mainly for damaging the optic nerves or the chiasm; nevertheless, the increasingly improvement in the equipment and surgical techniques allows treatments with much less complications (Cappabianca, et al, 2002).
- Post-radiotherapy optic neuropathy. This is a minor problem nowadays because radiotherapy is an unusual treatment for these tumours, and also because of the improvement in the techniques using fractioned radiotherapy and protecting important structures such as the optic discs (Van den Bergh, et al, 2007).

3. Visual recovery prediction factors

During the last years different specialists involve in the management of pituitary adenomas have tried to establish prognostic factors of visual recovery after the treatment of these patients. To date there are several well recognize prognostic factors, such as the age of patients (the older the worse prognostic), the duration of the symptoms before the surgery, the size of the tumour (better prognostic in microadenomas) and the presence of pituitary apoplexy, which is a bad prognostic factor. From the ophthalmology point of view, several factors such as visual acuities less than 20/100 or a pale optic disc have been reported to determine a worse prognostic (Chhabra & Newman, 2006).

Although some cases show a severe visual impairment, it is not unusual to observe important early recoveries (1st week), intermediate recoveries (1-4 months) or even late recoveries in some patients (up to 36 months after surgery) (Kerrison, et al, 2000). This

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indicates that there must be other factors that determine different degrees of axonal affectation in different patients. One of the main current research lines in this field is actually seeking the diagnostic tools that allow us to predict the degree of axonal loss, and so the possibility of visual function recovery after the treatment.

During the last years, OCT has been used to establish and quantifying the axonal loss in several neurological disorders. OCT is a non-invasive tool that allows the retina to be directly approached as an appendix of the central nervous system. We can measure peripapillary retinal nerve fiber layer (RNFL) thickness, a parameter which has been found to be reproducible and useful for the diagnosis, prognosis and follow-up of optic nerve axonal damage in several neurological diseases, including pituitary adenomas (Moura, et al, 2007; Parisi, 2003; Sergott, et al, 2007; Kallenbach & Frederiksen, 2007; Toledo, et al, 2008; Noval, et al, 2006; Vessani, et al, 2009). (figure 6). OCT can be useful predicting

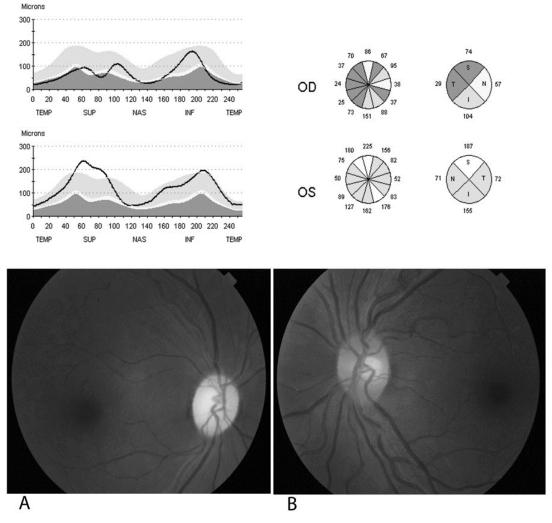


Fig. 6. Optical Coherence Tomography. Observe the retinal nerve fiber layer (RNFL) measurement in microns. A diagram is included to analyze the different sectors of the optic disc and peripapillar area. This example shows thinning of the RNFL affecting the right eye (OD) predominantly in the superior and temporal quadrants, the left eye (OS) shows normal results. The bottom of the image shows funduscopy of both eyes and demonstrates the optic disc atrophy of the right eye (A) while the left eye is normal (B).

the visual function recovery in patients with pituitary adenomas by measuring the axonal damage in the retina during the evolution of the disease (Ortiz-Perez, et al, 2009; Jacob, et al, 2008).

4. Conclusions

Pituitary adenomas are a frequent pathology with a wide spectrum of clinical features. These tumours should be managed between different specialists including general practitioners, endocrinologists, neurologists, neurosurgeons and ophthalmologists. Neuroophthalmological manifestations of pituitary adenomas are frequent and varied. They represent sometimes the onset symptoms in these patients. Many of the syndromes described above have an important diagnostic value due to their localizing information. Physicians must be aware about these syndromes in order to refer patients for ophthalmological assessments and establish an early diagnosis.

OCT is a new device used daily in ophthalmology clinics to study the retina and optic disc. This tool gives unique and new information about the axonal loss in patients with neurological disorders, including pituitary adenomas. OCT is easily performed, it has no side effects or contraindications, so it must be included in the routine examination of patients with hypophysis tumours.

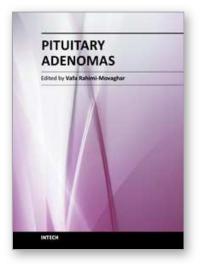
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Pituitary Adenomas Edited by Prof. Vafa Rahimi-Movaghar

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Pituitary Adenomas is a comprehensive book about the most common pathology of the pituitary gland in the sellar region. The book chapters include epidemiology, symptoms and signs, clinical, imaging, immunohistochemical and ultrastructural pathological diagnosis, therapeutic approaches and outcome of the functional and non-functional pituitary tumors. Therapies include medications, endoscopic transphenoidal and open surgeries; radiotherapy includes gamma knife radiosurgery. Visual symptoms has important and characteristic patterns which has discussed in one specific chapter. Endocrine secretion is another characteristic in 40% of pituitary adenomas. Therefore, another chapter presents it. Stereotactic radiosurgery and endoscopic surgery both have special role in recent decades. Thus, they have considered specifically, too. Authors expect to give excellent insight in pituitary adenoma to the book readers.

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