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PITUITARY ADENOMA (PRESENTATION OF THREE CASE STUDIES)

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Abstract

Pituitary tumors are among the most frequent cerebral tumors ecountered in clinical practice with an incidence of 15% of all intracranial tumors, most of them being adenomas. Prolactinomas are the most frequent pituitary adenomas caused by autonomic hyperproduction of prolactin by lactotroph cells. The incidence of prolactinomas varies with age and sex. About 1 in 10 000 people will develop a prolactinoma for which the clear cause is not known. Prolactinoma occurs in both sexes, but are more common in women.

Our First case study is a 35 years old female patient complaining profuse sweting, gaining weight, enlargment of hand and feet and intermitent headaches. Facial examination reveals an enlargment of supraorbitaly arches, prognatia, enlargment of the space between the teeth, as well enalargment of the ears, nose, lips and macroglossia. Enlargment of extremities were noted, as well as a change in voice, which was proved by the patient. After MRI examination was found a lesion with dimensions 3 x 2x 1.5 cm with moderate uptake of the contrast at a selar and supraselar possition. The lesion was distended to nearby structures withouth involvment of optic chiasma. Based on the laboratory data, physical examination and imaging results the diagnosis was Pituitary Grouth hormone secreting macroadenoma or Acromegalia.The patient started treatmentn with oral hypoglicemiants (Metformine 500 mg) and rezectional transsphenoidal surgery was sugested (TSS).

In our second case we had a 17-year-old girl with menarche at the age of 14, irregular cycle (every 6 months) and menstrual pain. She was admitted to our clinic for further examination. Ultrasound of ovary and uterus resulted normal, but the laboratory examination resulted with hyperprolactinemia. MRI of the head revealed a pituitary lesion 1.0 x 1.2 cm, with displacement of the left pituitary infundibulum and with the aspect of pituitary macroadenoma. After treatment to restrict the tumor, the patient underwent transnasal, transsphenoidal surgery. The intervention removed the pituitary macroadenoma and the postoperatory MRI confirmed the removal. The patient is clinically well.

The third case was a young woman of 34 years old who was presented at our clinic with an irregular cycle (every 6 month). Laboratory examination and imaging confirmed our suspect of hyperprolactinemia and pituitary macroadenoma as a 1.5 x 1.7 cm mass, which was exerting pressure on the optic chiasma. After non-invasive treatment the patient went through transsfenoidal surgery, but her hormonal level were still unstable. After two years she went through another endoscopic surgical intervention, which was followed by stabilization of hormonal levels with the exception of GH, which remained low. Four days after surgery the patient developed pneumococcal meningitis which was treated sucessfully. Other than the impossibility of another pregnancy, the patient is feeling well today.

Introduction

Pituitary tumors are among the most common cerebral tumors in clinical practice with an incidence of 15% from all intracranial tumors where adenomas represent the majority. Pituitary adenomas are more frequently reported in females than in males in an average report 3: 1 (1).

Most pituitary tumors occur in adults, but they can also be encountered in children and elderly people. The average age of their appearance is 37 but there are tumors that appear frequently in patients over 60 years old, such as non-secretory tumors and acromegaly which is commonly seen in the fourth and fifth decade of life (2).

The mortality rate associated with pituitary tumors is low. In general, thanks to the early appearance of clinical signs their early detection is possible as well as their quick and efficient treatment. Some of the most dangerous complications of these tumors are the neurological ones, like permanent vision loss, post-treatment recurrences, metastases (even though they are very rare) or pituitary apoplexy that may result fatal. It should also be taken into consideration the consequences of the hormonal overproduction that depends on the specific by-product or over production of a hormone or several hormones from the related tumor (3).

Based on their size, pituitary adenomas can be divided into micro adenoma (<1 cm) and macro adenoma (>1 cm). They can also be classified according to the properties after haematoxylin-eosin staining in histopathological preparations, such as chromophobic and chromophilic (acidophilic or basophilic) tumors. Corticotropic adenomas are usually basophilic, prolactinomas and GH-secreting tumors are acidophilic, TSH-secreting, Gonadotropin-secreting tumors or non-secreting tumors are generally chromophobic. Pituitary adenoma may result in overproduction of one or more hormones as a consequence of the increased gene expression of the producing cells or in the suppression of this expression as a consequence of the suppressive effect of tumor cells on healthy pituitary cells. They are benign tumors that in the case of hormonal overstimulation give clinical manifestations of prolactinemia, acromegaly, Cushing syndrome or hyperthyroidism. Likewise, they can develop silently and be diagnosed only as a result of the mass effect into pituitary selar body. The neoplastic features of adenomas, whether they are or they are not secretory, are similar. They have a slow mitotic rate and mostly spread localy with poor metastasing capabilities. The greatest risk comes from their local growth and the pressure they exert on the structures located nearby. Depending on their extent, adenomas can be intra pituitary, intraselar or diffuse with an extension to the surrounding pituitary tissues.

From the genetic viewpoint, pituitary adenomas are most often monogenic expressions and rarely originate from stem cells with multiple hormonal production. Most oncogene abnormalities involved in the pathogenesis of pituitary tumors are: abnormalities of G protein, ras gene, p53 gene mutations and mutations that characterize the multiple endocrine neoplasia syndrome. One of the newly discovered genes is gene-1 (PTTG-1) that serves as a marker of the malignancy classes in some endocrine tumors. This gene is known for regulating the cell division process and the forced expression of this gene causes the formation of pituitary tumors. This fact is documented in several experiments with mice (4).

Recent work suggests that pituitary tumor genesis is more heterogeneous than it was once thought. Dysfunctional adenomas and prolactinomas are associated with hyper methylation of p16 gene, and corticotropic secretion tumors express galectin-3 (Gal-3), a gene involved in cell growth and the control of apoptosis (5) (6). Inhibition of Gal-3 may serve as a molecular therapeutic target in the future. Mutations of the Aril Hydrocarbon Receptor Protein gene (AIP) may be present in some cases of inherited gigantism and acromegaly, as well as other pituitary tumors (7). For most benign tumors, the presence of several factors involved in the tumor genesis can determine their degree of growth and aggressiveness. For example, the presence of p53 corresponds to the most aggressive type of tumor.

Clinical manifestations are due to the local effect of the mass and endocrine manifestations outcome from over secretion of tumor cells. Pituitary adenomas, with some exceptions, are not under the control of hypothalamic controling factors by making it difficult to selflimit themselves from the body.

Another adenoma-related phenomenon is their compressive effect on the structures around the pituitary gland. To evaluate this process, recently, physical measurements of intra chiasmatic pressure were performed by special cadaveric catheters to imitate the pituitary mass pressure. In this study, it was noted that suppression was bigger in the center rather than lateral chiasma, confirming the bitemporal hemianopsia which is found in these tumors.

Histology

Histological examination of pituitary adenomas is based on type of cell which causes the adenoma and are classifies as Somatotropes, Lactotropes, Corticotropes, Gonadotropes, Thyrotropes and others (9).

Adenoma cells are irregular in size and have atypical morphology with prominent nucleoli, poorly preserved cytoplasm which do not stain properly in H&E paraffin sections (10). It may be acidophilic, basophylic or chromophobe and usually uniform in their staining. The tumors have a thin reticulin network which distinguishes the tumor from normal tissue which is heterogenic in staining (basophils, acidophils and chromophobes) and the reticulin network is not as extensive as in the tumor.

Prolactin secreting adenoma is made of medium size cells with chromophobic or slightly acidophilic cytoplasm. They have oval nuclei positioned in the centre (sometimes small nucleoli may be present). 20% of prolactionomas display microcalcifications. Calcifications alone or associated with amyloid bodies, which are often seen in prolactinomas, are not pathognomonic of these

adenoma. Adenoma cells are characterized by a prominent RER network, Golxhi complex and small secretory granules (150 – 300 nm). Irregular exocytosis is also typical of these cells.

Signs and symptoms

The symptoms associated with pituitary adenomas are related to a number of factors. They mostly depend on the cell type and in the secretory capabilities of the cell causing the tumor. So the tumor may be functional or non-functional. In prolactinomas the pituitary tumor increases the production of prolactin leading to menstrual cycle disorders (amenorrhea, oligomenorhea), galactorhea, low libido and fertility in females. In males the high levels of prolactin cause a lowering of Testosterone levels leading to lower libido, erectile dysfunction, gynecomastia and infertility (11).

Diagnosis

In functional pituitary tumors is done by measuring the levels of hormones (basal prolactin level, TSH, free T4, FSH, LT, Testosterone levels in males, Estradiol levels in females, IGF-1). These are some of the most important tests in every patient suspecting a pituitary adenoma. They may confirm or exclude a functionally active adenoma as well as confirm a pituitary failure.

Imaging - pituitary tumors are diagnosed using MRI which has the highest resolution from all the other imaging methods. This method is effective for tumors measuring more than 4 mm, but in some cases, a powerful 3T (Tesla) MRI machine may diagnose even smaller tumors. MRI remains the most effective imaging method for pituitary adenomas but in some cases CT may also be used.

Treatment

Treatment of pituitary adenomas depends on a number of factors:

1. The type of hormone secreted by the tumor.
2. Size of the tumor
3. Infiltration of the tumor in the neighbouring structures
4. Age and overall health status of the patient

Possible therapeutic interventions are medications, surgery and radiation therapy. Purpose of treatment is to relieve the local pressure caused by the tumor mass on the surrounding structures and lowering the hormone hypersecretion caused by the functional tumors while preserving the normal pituitary functions.

For patients with prolactinomas first line of treatment is medication with Dopamine agonists (12). The most commonly used are Bromocriptine and Cabergoline, which is mostly used in patients resistent to Bromocriptine. Transsphenoidal surgery is the second line of treatment for patients who are intolerant or resistent to Dopamine agonists. Radiations therapy is used as a third line of treatment for patients with recidival or recurrent prolactinomas after medications and/or surgery.

Material and Methods

Case study

Results

First case study

Patient R.S., 35 years old is presented near the Endocrynology service complaining for profuse sweting, gaining weight, enlargment of hand and feet and intermitent headaches. Complains have started to apear in a period of 4 -5 years, but have become more evident in the last months.

During physical examination the overall patient health status is well. Neurological examination shows no signs of involvment. She is conscient and without alteration in mental status. Skin is coloured, no bleeding disorders or cyanosis. During the cardiovascular examination heart rate is normal (84/min) and blood preasure is 138/90 mmHg. Vesicular respiration with a respiratory frequence 18/min. There is no pain or palpable mass in abdominal examination. Lymphatic system seems untouched. Facial examination

reveals an enlargment of supraorbitaly arches, prognatia, enlargment of the space between the teeth, as well enalargment of the ears, nose, lips and macroglossia. Enlargment of extremities were noted, as well as a change in voice, which was proved by the patient.

Blood Count		***Reference (female, age 30 – 35 years old)***
Heamoglobin (Hb)	11.6 g/dl	12 – 15
Rbc	4 800 000/mm3	4 200 000 – 5 400 000
Wbc	5200/mm3	4000 – 10 000
Platelets	265 000/mm3	150 000 – 400 000
Biochemical laboratory results		
Glicemia	**126 mg/dl**	**65 – 110**
Total Bilirubin	0.8 mg/dl	0.3 – 1
Glucuronated Bilirubin	0.2 mg/dl	< 0.3
AST/SGOT	31 U/l	5 – 30
ALT/SGPT	35 U/l	5 – 30
Alkalin Fosfatase (ALP)	**192 U/l**	**50 – 100**
Urea	11 mg/dl	6 – 20
Kreatinin	0.2 mg/dl	0.8 – 1.3
Natremia (Na)	141 mEq/l	135 – 145
Kalemia (K)	4.5 mEq/l	3.5 – 5
Calcemia (Ca)	11 mg%	8.9 – 10.1
Magnezemia (Mg)	1.6 mg/dl	1.7 – 2.4
Trigliceride	90 mg/dl	50 – 150
Total Kolesterol	150 mg/dl	50 – 200
Hormonal levels		
Grouth Hormon (GH)	**45 ng/ml**	**0 – 5**
IGF-1	**860 ng/ml**	**73 – 244**
Follicle Stimulating Hormone (FSH)	1.26 mU/ml	1 – 10
Luteinising Hormon (LH)	0.06 mU/ml	1.9 – 12.5 (folikular phase of the cycle) 8.7 – 76.3 (ovulation) 0.5 – 16.9 (luteal phase of the cycle)
Testosterone	0.18 ng/ml	1.5 – 7
Prolaktin (PRL)	30 ng/ml	2 – 29
Tireo Stimulating Hormon (TSH)	5.7 mcU/ml	0.5 – 5
Thyroid Hormon T3	130 ng/dl	75 – 200
Thyroid Hormon T4	7.1 mcg/dl	4.6 – 12

Imaging:

Using MRI was found a lesion with dimensions 3 x 2x 1.5 cm with moderate uptake of the contrast at a selar and supraselar possition. The lesion was distended to nearby structures withouth involvment of optic chiasma.

Diagnosis

Based on the laboratory data, physical examination and imaging results the diagnosis was:
Pituitary Grouth hormone secreting macroadenoma or Acromegalia

Treatment

The patient started treatmentn with oral hypoglicemiants (Metformin 500 mg) and rezectional transsphenoidal surgery was sugested (TSS).

Second case: Patient A.D. 17 years old female

During history the patient refers menarche at the age of 14, with menstruation every 6 months, oligomenorhea associated with menstrual colics.
Ultrasound examination of uterus and ovaries whithout structural changes.
She was put on treatment with Jaz 2 cycles. The cycle was improved for as long as she was under treatment.
After 4 months she is presented with secondary amenorhea, malaise, weakness and anorexia.
Laboratory hormonal examination reveals hyperprolactinemia and she is refered to the endocrinologist and was latter admited in the Endocrinology department at the QSUT.
MRI reveals a pituitary lession measuring 10 x 12 mm, with displacment of the pituitary infundibulum to the left, with the aspect of pituitary macroadenoma.
Hormon laboratory test results:

- PRL: 346 (2,54-23-03)
- TSH: 0,59 (0,4-4,2)
- PRL: (18.4.17): >150
- GRAN- 0,147

During May 2017 the patient went through transsfenoidal surgery. The tumor mass was removed and the removal was confirmed by post operator MRI.
After the intervention the hormonal levels were as follows:
PRL: 121 (1,190-25), TSH: 0,44, COR: 6,2
The patient is clinically well.

Third case: Patient I.S. 34 year old female

During 2017 she was presented to our clinic with menstrual cycle distrurbances. Even after treatment she was having a cycle every 6 months.
Uterus and ovaries resulted normal after ultrasound examination. Hormonal laboratory results showed hyperprolactinemia.
An X-Ray of sela turcica resulted without changes in shape or size.
We started Cabergoline and during a three year period the cycle and plasma prolactin levels were normal. During 2009 the patient had a normal pregnancy and one year after that she refers serious galactorhea. MRI examination reveals a pituitary adenoma. During 2010 prolactinemia was found elevated >200 ng/ml.
MRI results: Selar formation with dimensions 1.5 x 1.7 cm, slightly compressing the optic chiasm. After contrast injection the selar lession displays a delay in absorbance compare to the normal pituitary tissue. Cerebral tonsils are normal, basal cisternae free, without brain lessions.
Conclussion: Pituitary macroadenoma.
Hormonal levels:

- GH: 47,9 ng/ml (<10), IGF1-July ng/ml (107-310)
- October 2010, she undergoes transsphenoidal surgery.

October 2010: GH: 10,1 ng/ml, IGF1: 1485 ng/m, PRL: 43,5 ng/ml.
Cabergoline was initiated at 0.5 mg, 1 tablet every 2 days.

- December 2010: TSH: 0,73 UI/L, Urin density: 1010, Cortisolemia: 185 mg/ml
- January 2011: GH: 19,2, IGF1: 796 ng/ml
- March 2011: IGF1: 987 ng/ml,

Sandostatine was recomanded and administered ina clinic outside the country.

September 2011 – MRI reveals normal cerebral tonsils, free basal cisternae, no cerebral lessions. Pituitary gland is enlarged in the supraselar region, without contat with optic chiasma and with hemoragic areas inside. The aspect is typical of macroadenoma. Patient refers changes in hormonal levels associated with acromegalia.
February 2012 – She travels to France where she has another endocopic nasal surgery. On the fourth day after the intervention the situation was complicated with Pneumococcal meningitis. She was treated with antibiotic therapy and the engorged areas were drained and irrigated.
After treatment the patient was recovered from meningitis, hormonal levels were back to normal with the exeption of Gonadotrops which were low. She was recomended corticotherapy and physical therapy for the motor rieducation of the lower extremities.

Discussion

In the case of suspection of pituitary tumors, clinical signs and symptoms, hormonal levels and MRI examination are suficient in diagnosing the tumor and follwing up treatment.

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