

# INTRASELLAR PRESSURE AND TUMOR VOLUME IN PITUITARY TUMOR

## Relation study

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**ABSTRACT** - *Objective:* To determine if there was a relationship between intrasellar pressure (ISP) and pituitary tumor volume. *Method:* Between August 2002 and May 2004, 60 patients aged between 13 and 75 years old (39 males), having a pituitary adenoma were submitted to an endoscope transseptal approach. During the surgery and before tumor resection, 2 mm of the sella's floor were removed and a 1.5 mm dural opening made to place a transducer into the pituitary adenoma. The transducer was connected to a pressure monitor. *Results:* The intrasellar pressure ranged from 2-51 mmHg and was measured based on the classification of Hardy-Vezina. The most elevated was in the type II macro adenomas with 32.6 mmHg, sharply superior to the value of a normal intracranial pressure. *Conclusion:* These values showed that the macroadenomas confined to the sella, without destruction of the floor and integrity of the diaphragm, type II of Hardy-Vezina, presented a value of ISP much higher than intra-extrasellar macroadenoma's.

**KEY WORDS:** pituitary adenoma, intrasellar pressure, endonasal approach.

### Relação entre pressão intra-selar e volume de tumor de hipófise

*Objetivo:* Determinar se existia uma relação entre a pressão intraselar (ISP) e o volume de tumor de hipófise. *Método:* Entre agosto de 2002 e maio de 2004, 60 pacientes com idades variando entre 13 e 75 anos (39 homens), portadores de adenoma hipofisários foram operados por via transesfenoidal. Durante o ato cirúrgico e antes da ressecção do tumor, uma osteotomia de 2 mm foi realizada no assoalho selar e uma abertura de 1,5 mm na duramater para a introdução de um transdutor dentro do tumor. O transdutor foi conectado a um monitor de pressão e esta foi medida por 2 minutos. *Resultados:* A pressão intra-selar variou entre 2-51 mmHg e a correlação entre tamanho do tumor e ISP foi baseada na classificação de Hardy-Vezina. A média da ISP mais elevada foi encontrada nos macroadenomas tipo II com 32,6 mmHg, nitidamente superior a pressão intra selar normal. *Conclusão:* Estes valores mostram que os macroadenomas confinados a sela sem destruição do assoalho selar e com integridade do diafragma, classificados como tipo II de Hardy-Vezina, apresentam uma ISP muito superior aos outros adenomas.

**PALAVRAS-CHAVE:** adenoma hipofisário, pressão intra-selar, via transesfenoidal.

There are studies in the literature correlating intrasellar pressure (ISP) and adenoma blood flow<sup>1</sup>, ISP and stalk compression syndrome<sup>2</sup>, ISP and endocrine function<sup>3,4</sup>, ISP and headaches<sup>3</sup>, pituitary volume and headache<sup>5</sup>, ISP and pituitary tumor apoplexy<sup>6</sup>, but there are no specific studies correlating ISP and tumor volume.

The walls of the sella turcica are a relatively rigid structure and under normal circumstances, may serve to protect the pituitary gland from trauma and surrounding pressure fluctuations. The growth of a tumor within the sella, a normally inelastic space, is likely to cause an increase of ISP. It has been conjec-

tured that relatively small increases of ISP may disturb anterior pituitary perfusion and endocrine function because of the low input pressure of the feeding portal veins<sup>3</sup>. Normal ISP is not known but it is unlikely to exceed normal intracranial pressure (ICP). The ISP has been shown to be elevated in patients with pituitary tumors<sup>3</sup>. It has been proposed that relatively small increases of ISP may disturb anterior pituitary perfusion. The highest pressures were recorded in tumors with parasellar invasion irrespective of the size and extension and there were no correlation between the level of raised ISP and the tumors size<sup>3</sup>. Our study, in the contrary, postulates that

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the highest ISP is found in macroadenomas confined to an enlarged sella without disruption of the floor and with integrity of the diaphragm as type II tumor of Hardy Vezina<sup>6</sup>.

The objective of this study is to determine if there is a relationship between ISP and pituitary tumor volume.

## METHOD

Between August 2002 and May 2004 sixty consecutive patients (39 males) with pituitary adenomas were operated by transnasal transsphenoidal endoscopic surgery and had their ISP measured during surgery for pituitary adenoma at our institution. Their age was between 13 and 75 years old. Among the 60 cases, studied, 42 (70%) were functional adenomas (eighteen producing adrenocorticotropin hormone, fourteen producing growth hormone, six producing prolactin hormone and four cases of plurihormonal adenomas) and eighteen null cells adenomas. All patients were ambulatory. No patients were using glucocorticoids or had pituitary apoplexy, but some patients had adenomas with cystic component. The patients with hormonal hypopituitarism, the compensation usually begins in the transoperative period. The study was approved by the Institutional Review Board of General Hospital of Fortaleza, an informed consent was obtained from each patient.

All patients underwent pituitary computerized tomography (CT) and magnetic resonance image (MRI) at 1.5 T. The MRI examination included coronal and sagittal T1-weighted spin-eco sequences with a maximum section thickness of 3 mm, before and after intravenous administration of a gadolinium-based contrast medium. For the estimation of the tumor volume, it was assumed that the pituitary tumors had an ellipsoid form<sup>5,7-9</sup>. If the tumor was large and multilobed, the tumor volume was assumed to consist of separated ellipsoids and the sum of each volume was calculated.

Tumors were subdivided according to radiological classifications of Hardy and Vezina<sup>6</sup>. The tumors were classified as microadenoma grade 0 where they weren't visible on imaging. Immunohistochemical characteristics of tumor were available in all patients. The tumor volume distribution classification is showed in the Table.

Pre-operative pituitary function evaluation was performed in all patients, and included basal serum free T4, free T3, thyroid stimulation hormone, follicle-stimulating hormone, luteinizing hormone, testosterone (men), cortisol levels on multiple days, adrenocorticotropin hormone, prolactin, growth hormone and somatomedin-C and a glucose tolerance test with GH.

The transsphenoidal exploration was carried out under

general anesthesia with normotension and normocapnia. The pituitary sella's floor was exposed through a transnasal transseptal approach assisted by endoscope<sup>10</sup>. On entering the sphenoid air sinus a 2-mm diameter window of the bone sella's floor was removed and a 1.5 mm dural opening was made to allow the transducer placed into a needle in the tumor mass without extravasation of intrasellar content. Once the transducer placed the needle is taken off and the ISP measured. In some patients with cystic component a careful attention is made for extravasations of tumor component. If there were tumor component extravasations, the ISP measurement would be stopped and the patient wouldn't count. The fiberoptic transducer is located at the tip and has a 1.3 mm diameter. Sixty seconds later, after a stable pressure obtained, the pressure was recorded, the transducer removed and the tumor resection initiated. We used the Coodman Intracranial Pressure Monitoring Kit (Camino Laboratories San Diego, CA) to determine the ISP. The kit uses a fiberoptic transducer connected to a pressure monitor.

The statistic analysis was done using the test of Levene to see the homogeneity of variances. The F test was done to know if there was a difference between the five intrasellar pressure median groups. The individual comparisons between the pairs of the five group of ISP were done using the multiple comparisons test of Bonferroni. Statistic analysis using the F test was done with the prolactin medium in each group of patients (Cushing, acromegaly and null cells adenoma). The ISP was also compared into the four group of pathology (acromegaly, Cushing, prolactinoma and null cells adenoma). Variables with significant probability values ( $p < 0.05$ ) were considered a possible significant. Statistical evaluation was performed with commercially available statistical software (SPSS version 10.0).

## RESULTS

Tumor volume was measured in all adenomas and varied between 0 cm<sup>3</sup> (in six patient with clinical and laboratorial diagnosis of Cushing's disease, but with no radiological image) and 134.5 cm<sup>3</sup> in a non-functioning pituitary adenoma with a cystic component. The tumors of this series were solid in 51 patients (85%) and had a cystic component in 9 (15%).

The ISP was measured in all 60 patients and ranged from 2-51 mmHg with mean ( $\pm$ sd) of 18.7 $\pm$ 10.8 and a median of 16 mmHg (Fig 1). The test of homogeneity of variances Levene Statistic showed significant (1.639  $p=0.178$ ) the amostrage of ISP measurement. The median comparison of the five groups of ISP showed all different (F 17.69  $p=0.001$ ). The statistic

Table. Tumor volume distribution in Hardy-Vezina classification.

Hardy-Vezina's Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No. of Patients	6	12	12	14	16

study was done to know the specific pair-wise analyses and showed that ISP of group 2 of Hardy-Vezina was different in the pair comparison of all other group (0 and 2  $p=0.026$ ; 1 and 2  $p=0.0001$ , 2 and 3  $p=0.0001$ ; 2 and 4  $p=0.0001$ ).

Six patients showed immunohistochemical characteristics of prolactin adenoma and were excluded from the analysis of correlation between ISP measurements and serum prolactin. The prolactin serum was ranged from 5-57  $\mu\text{g/L}$  with mean of  $24.3\pm 8.2$  and a median of 25.1  $\mu\text{g/L}$ . The statistic analysis between ISP and prolactin in the group of patients with acromegaly ( $R=0.767$   $p=0.075$ ), Cushing ( $R=0.588$   $p=0.491$ ) and null cells adenoma ( $R=-0.161$   $p=0.600$ ) do not show significant statistic variation.

In the analyses of different immunohistochemical characteristics types of pituitary tumors in this series and the ISP register, indicate the absence of relationship between ISP and tumor type ( $R=4.543$   $r=0.022$ ).

## DISCUSSION

The measurement of ISP is simple, reproducible and can be done using standard equipment as the same for intracranial pressure monitoring. The normal ISP is unknown but is unlikely to exceed the ICP. There are no studies of ISP in patients without intrasellar tumor in the literature, but some studies<sup>1,4</sup> showed that when ISP was measured in patients with microadenoma and empty sella the ISP were  $13,5\pm 3$  mmHg. In our series we measured the ISP in six pa-

tients with Cushing's disease, and no tumor found in the MRI, but with petrous sinus sample confirmation the pituitary origin of the disease. The ISP measured in these six cases was 15 mmHg, 6 mmHg and 2 mmHg, 8 mmHg, 2 mmHg and 8 mmHg respectively, with an average of  $6.83\pm 6.5$  mmHg, median of 7 mmHg. The observations in others studies suggest that normal ISP is of the order of 10 mmHg<sup>4</sup>.

The perfusion of the anterior pituitary depends on the balance between the portal venous input and the local tissue pressure. The structure of the long portal vessels is similar to that of peripheral veins<sup>11-13</sup> and even a minor elevation in the ISP would reduce blood flow to the pituitary. Normal portal venous pressure is unlikely to greatly exceed systemic venous pressure. The perfusion pressure of the anterior pituitary must be considerably lower than the arterially supplied tissue and may be seriously compromised by a relatively small ISP's rise<sup>2</sup>. The observation of large tumors with high ISP and no significant compromise in the pituitary function is probably due to a direct extraportal arterial supplies<sup>10</sup>.

The ISP was measured separately in the patients according to Hardy-Vezina's classification, and it was verified that the ISP was more elevated in the macroadenomas type II with median of 32.6 mmHg, sharply superior to the normal ICP. In the adenomas type 0 the ISP was (7 mmHg), in I (19.2 mmHg), in II (32.6 mmHg), in III (11 mmHg) and in IV (14.8 mmHg) (Fig 2). These values show that the macroadenomas confined into the sella, without destruction of the

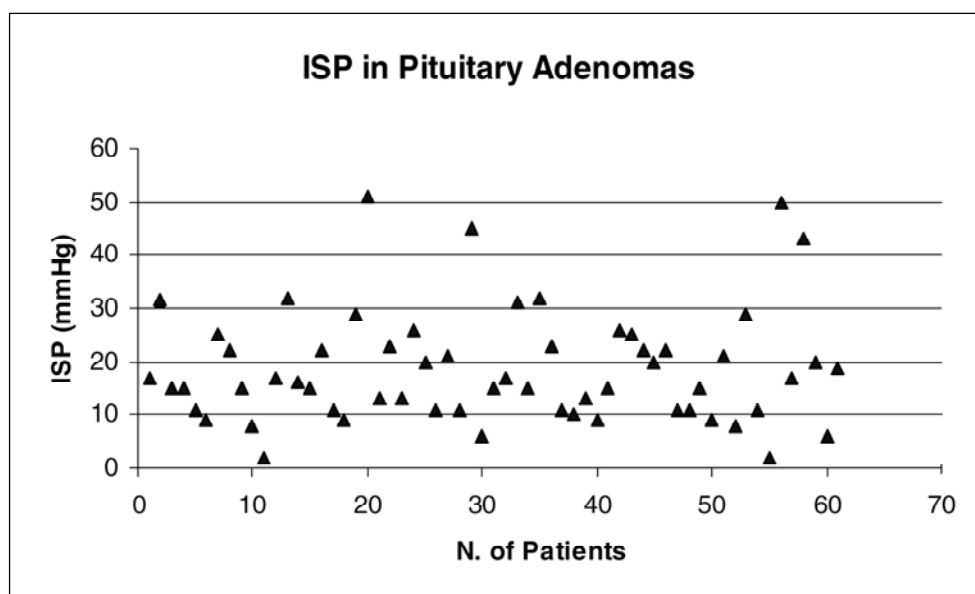


Fig 1. ISP in sixty patients of the series.

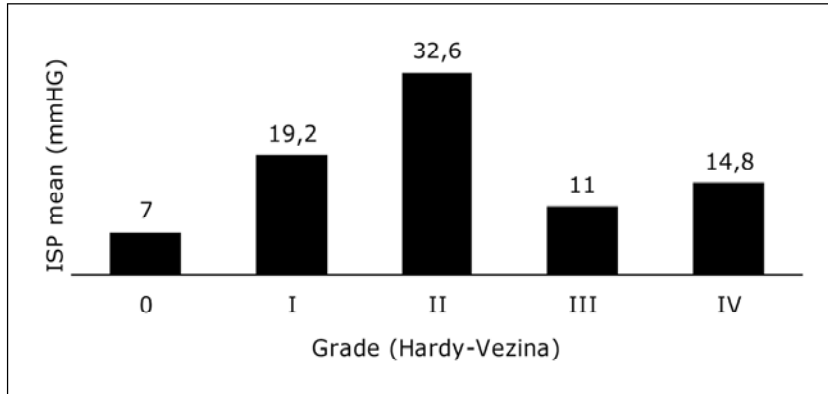


Fig 2. Shows the distribution of tumor grade and median ISP value according to the Hardy-Vezina classification.

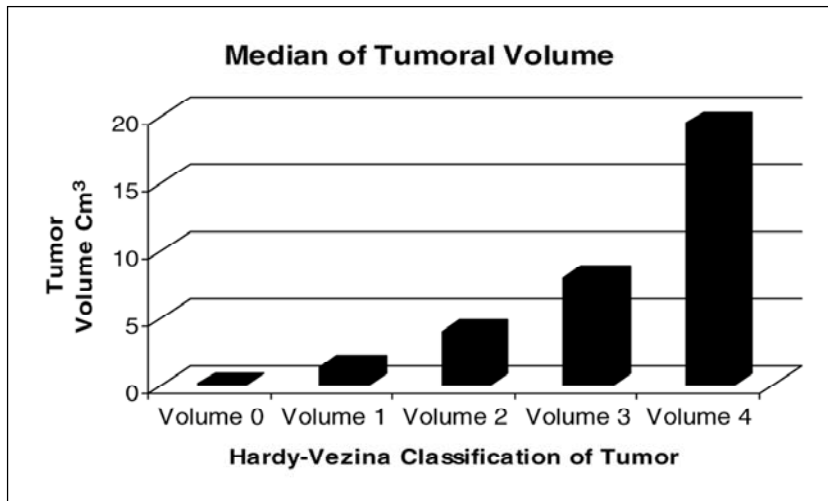


Fig 3. Shows the distribution of medium tumor volume according to the Hardy-Vezina classification.

floor, and integrity of the diaphragm, presented an ISP much higher than those tumor with both intra and extrasellar extension (Fig 3). It does not seem coherent, but the explanation can be the following: while the tumor is a microadenoma (grade 0 or 1) it will be contained inside the sella, a closed cavity. The growth of the tumor inside this cavity will increase ISP progressively. In the moment that the sella is no more competent to contain the pituitary and the tumor, there will be a rupture of the content of the sella into the cranial cavity and/or the sphenoid sinus. In case of an almost ruptured sella, there will be an ISP in its maximum value. In this series, this value was 51 mmHg. In the series of Arafah<sup>3</sup> this value reached 60 mmHg and in the series of Kruse<sup>1</sup> it was of 62 mmHg. When the tumor leaves the limits of the sella cavity, the universe of the adenoma in terms of ISP is no more the sella, but the cranial cavity. At this

time ISP tends to be equal to ICP, having a decrease in relation to ISP of the intrasellar adenomas.

When there is an important growth of the adenoma, the ISP can influence the ICP, mainly if there is a blockade of the cerebral blood flow. If the adenoma does not grow towards the diaphragm, but down, destroying the floor of the sella, (free tumor within the sinus), the ISP will tend to fall, as a consequence of equilibration with atmospheric pressure via the sphenoid air sinus<sup>4</sup>. An important factor involved in the genesis of ISP, is the speed of the tumor growth and the ability of the sella's walls to modulate this growth. In general, patient with fast growing tumor confined to the sella (pituitary apoplexy, metastases tumors), are more susceptible to present higher ISP than those with slow growing tumor.

In patients with hyperprolactinemia and no pro-

lactin secretor tumor, there were no correlation between the ISP and the level of prolactine.

In patients with hypopituitarism there is also no correlation between this situation and ISP.

In patients with predominantly cystic tumors and with thin walls there are possibilities of error in introducing the transducer into the cystic part of the tumor. The exit of the cystic liquid may give a negative false result.

In conclusion, the pituitary adenomas classified as grade II of Hardy-Vezina are probably the tumor with the highest ISP, higher than the normal ICP.

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