

MAGNETIC RESONANCE IMAGING OF CAVERNOUS SINUS INVASION BY PITUITARY ADENOMA

Diagnostic criteria and surgical findings

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ABSTRACT - This study used MRI to define preoperative imaging criteria for cavernous sinus invasion (CSI) by pituitary adenoma (PA). MR images of 103 patients with PA submitted to surgery (48 with CSI) were retrospectively reviewed. The following MR signs were studied and compared to intraoperative findings (the latter were considered the gold standard for CSI detection): presence of normal pituitary gland between the adenoma and CS, status of the CS venous compartments, CS size, CS lateral wall bulging, displacement of the intracavernous internal carotid artery (ICA) by adenoma, grade of parasellar extension (Knosp-Steiner classification) and percentage of intracavernous ICA encased by the tumor. Statistical analysis was performed using chi-square testing and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were obtained for each MR finding. The following signs have been found to represent accurate criteria for non-invasion of the CS: 1- normal pituitary gland interposed between the adenoma and the CS (PPV, 100%); 2- intact medial venous compartment (PPV, 100%); 3- percentage of encasement of the intracavernous ICA lower than 25% (NPV, 100%) and 4- medial intercarotid line not crossed by the tumor (NPV, 100%). Criteria for CSI were: 1- percentage of encasement of the intracavernous ICA higher than 45%; 2- occlusion of three or more CS venous compartments and 3- occlusion of the CS lateral venous compartment. The CS was very likely to be invaded if the inferior venous compartment was not detected (PPV, 92,8%), if the lateral intercarotid line was crossed (PPV, 96,1%) or if a bulging lateral dural wall of the CS was seen (PPV, 92,3%). The preoperative diagnosis of CSI by PA is extremely important since endocrinological remission is rarely obtained after microsurgery alone in patients with invasive tumors. The above mentioned MR imaging criteria may be useful in advising most of the patients preoperatively on the potential need for complementary therapy after surgery.

KEY WORDS: magnetic resonance imaging, pituitary adenoma, cavernous sinus, invasion, microneurosurgery.

Ressonância magnética da invasão do seio cavernoso por adenomas hipofisários, critérios diagnósticos e achados cirúrgicos

RESUMO - Este estudo utilizou exames de RM para definir critérios pré-operatórios de imagem para invasão do seio cavernoso (ISC) em adenomas hipofisários (AH). As imagens de RM de 103 pacientes com AH tratados cirurgicamente (48 com ISC) foram revisadas retrospectivamente. Os seguintes sinais de RM foram estudados e comparados aos achados intraoperatórios (considerados o padrão-ouro para invasão do seio cavernoso): presença de glândula hipofisária normal interposta entre o adenoma e o SC, situação dos compartimentos venosos do SC, tamanho do SC, abaulamento da parede lateral do SC, deslocamento da artéria carótida interna (ACI) intracavernosa pelo adenoma, grau de extensão paraselar (classificação de Knosp-Steiner) e porcentagem de envolvimento da ACI intracavernosa pelo tumor. A análise estatística foi realizada utilizando o teste de qui-quadrado e a sensibilidade, especificidade, valor preditivo positivo (VPP) e valor preditivo negativo (VPN) foram obtidos para cada critério de imagem. Os seguintes sinais representaram critérios precisos de ausência de invasão do SC: 1- presença de glândula hipofisária normal interposta (VPP de 100%); 2-compartimento venoso medial visível (VPP de 100%); 3-porcentagem de envolvimento da ACI intracavernosa inferior a 25% (VPN de 100%); 4-não cruzamento da linha intercarotídea medial pelo tumor (VPN de 100%). Os critérios definidos para invasão do SC foram: 1-porcentagem de envolvimento da ACI intracavernosa maior que 45%; 2-não visualização de 3 ou mais compartimentos venosos do SC; 3-não visualização do compartimento venoso lateral do SC. A presença de invasão do SC era muito sugestiva quando o compartimento venoso inferior não era visível (VPP de 92,8%), a linha intercarotídea lateral era cruzada (VPP de 96,1%) ou quando a parede lateral do seio cavernoso estava abaulada (VPP de 92,3%). O diagnóstico pré-operatório de ISC por adenomas hipofisários é extremamente importante, pois a remissão endócrina é raramente obtida em pacientes com tumores invasivos tratados apenas por microcirurgia. Os critérios de imagem acima mencionados podem ser úteis para alertar a maioria dos pacientes no pré-operatório da necessidade potencial de tratamento complementar adjuvante após a cirurgia.

PALAVRAS-CHAVE: ressonância magnética, adenoma hipofisário, seio cavernoso, invasão, microneurocirurgia.

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Pituitary adenomas (PA) are benign tumors, which usually grow causing compression of adjacent anatomical structures and sellar enlargement. However, some PA may infiltrate adjacent tissues, such as the sphenoid sinus, diaphragma sellae and cavernous sinus (CS). These adenomas have a more aggressive biological behavior and are considered to be invasive. Ten percent of PA invades the CS^{1,2}. The surgical morbidity and mortality might be increased in these patients and tumor resection is usually partial, yielding a low rate of endocrinological remission. Adjuvant treatment (radiotherapy or medication) is often necessary in these patients. The preoperative diagnosis of cavernous sinus invasion (CSI) is important in the planning of surgical and adjuvant treatment strategies.

The clinical signs of CSI occur only late in time, so that its precocious diagnosis can only be performed through imaging. MRI is the best technique to evaluate the sellar region, but it is not always accurate to precisely demonstrate the CS/pituitary interface. Total encasement of the internal carotid artery (ICA) by the tumor has been classically defined as a sign of invasion on MRI, but this also occurs only late during tumor progression. The diagnosis of CSI is usually performed at surgery. Experienced neurosurgeons can easily distinguish between normal and abnormal dural walls. Some authors¹⁻⁶ have tried to define imaging criteria for CSI using anatomical parameters, such as the intracavernous ICA and the CS venous compartments; they have also compared imaging and surgical findings.

The purpose of this paper was to investigate MRI criteria that could potentially provide reliable preoperative information on the presence of CSI.

METHOD

Clinical data related to the endocrinological syndrome, the presence or not of headache and surgical outcome were available for all patients. MRI findings of 103 patients (62 women, 41 man; age ranging from 13 to 75 years) with PA who underwent surgical treatment at Hospital Brigadeiro from March 1992 to August 2002 were retrospectively reviewed.

There were 47(45.5%) patients with acromegaly, 36 (35.0%) with Cushing's disease, 14(13.5%) with nonsecreting tumors, 3(3.0%) with prolactinoma, 2(2.0%) with gigantism and 1(1.0%) with TSH secreting adenoma.

All patients have MR examinations performed on 1.5T units. We analyzed gadolinium enhanced coronal images, obtained through T1-weighted spin-echo sequences with TR=500 and TE=20, a 192x256 acquisition matrix, a 20 cm field of view and 3 mm thick slices.

Two observers who had no knowledge of the surgical findings jointly analyzed the MR images. PA were classified by size in micro (<10mm) or macroadenomas (≥10mm). CS spaces were divided into 4 venous compartments as related to the ICA, as previously described⁷: the medial compartment, which is located between the ICA and pituitary fossa; the superior compartment, which is above the ICA; the lateral compartment, which is lateral to the ICA and the inferior compartment, which is under the ICA. The parasellar extension of the tumors was classified according the Knosp-Steiner classification¹: grade

0, when the adenoma did not cross the medial intercarotid line; grade 1, when the tumor passed the medial intercarotid line but did not cross the median intercarotid line; grade 2, when the tumor passed the median intercarotid line but did not cross the lateral intercarotid line; grade 3, when the adenoma passed the lateral intercarotid line and grade 4, when the ICA was totally encased by the tumor. The observers evaluated the following MRI features: 1. presence of normal pituitary gland between the adenoma and CS; 2. status of the CS venous compartments; 3. CS size; 4. CS lateral wall bulging; 5. displacement of the intracavernous ICA by the adenoma; 6. grade of parasellar extension (Knosp-Steiner classification¹); 7. percentage of the intracavernous ICA encased by the tumor, which was calculated measuring the angle of the artery's perimeter invaded by the tumor, using digital tools (Fig 1).

All patients underwent surgical treatment (99 patients through a transsphenoidal approach and 4 through craniotomy) by experienced neurosurgeons. The surgical findings were considered the gold standard for CSI. At surgery, invasion was defined by the direct observation through the surgical microscope of perforation of the medial wall of the CS or clear-cut CS dural involvement by the tumor. The presence of invasion of the duramater of the sellar floor and the extent of tumor resection (partial or total) were also documented. The majority of the procedures were recorded on tape.

MR and surgical findings were compared using χ^2 testing. $P < 0.05$ values were considered statistically significant. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each criterion. The criteria with best results in χ^2 testing were evaluated together by forward stepwise selection and the significant criteria ($p < 0.01$) were used to elaborate a predictive score of CS invasion. The probabilities of CSI were obtained with the significant criteria by the multiple logistic regression equation ($Y = \beta_0 + \beta_1.X_1 + \beta_2.X_2$).

The results of surgical morbidity and outcome were compared in patients with or without CSI or sellar floor's duramater involvement. The median follow-up time was 46 months (range 4 to 149

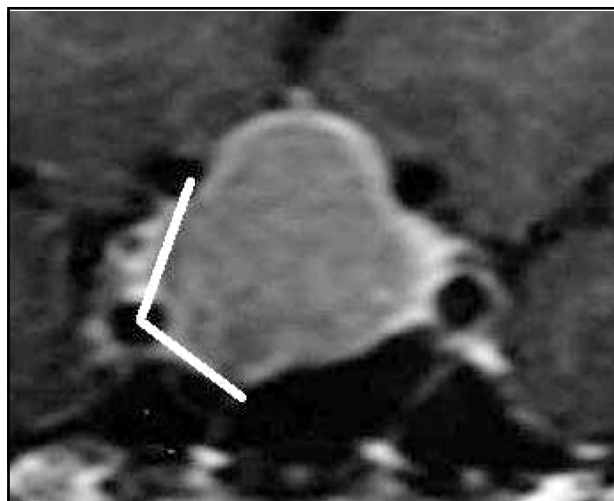


Fig 1. Coronal T1 MR image after contrast enhancement showing the technique for measurement of the percentage of encasement of the ICA by PA (right CS invasion).

months).

This study was approved by the Hospital Brigadeiro Ethics Committee.

RESULTS

Fifty-one (25%) of the 206 CS (103 patients) were unequivocally invaded by PA at surgery. The invasion was unilateral in 45 patients (23 at right side and 22 at left side) and bilateral in 3.

Among the 48 adenomas with CSI, 8 were microadenomas (16.5%) and 40 macroadenomas (83.5%). Twenty-two of the 55 adenomas without invasion were microadenomas (40.0%) and 33 macroadenomas (60.0%). This association was statistically significant ($p < 0.009$).

Complete surgical removal of the tumor was performed in 13 (27.0%) of the 48 patients with CSI and partial resection in 35 cases (73.0%). In noninvasive adenoma, total tumor resection was obtained in 47 patients (85.5%) and partial removal in 8 (15.5%) ($p < 0.001$).

Follow-up data were available in 98 patients (55 with CS and sellar floor dural invasion and 43 without invasion). Ten patients (18.0%) have been cured by surgical treatment within the invasive group; the remaining 45 patients (82.0%) required adjuvant treatment (radiotherapy in 37 patients and suppressive drug therapy in 24). In the group with non-invasive tumors, 27 patients (63.0%) have been cured by surgery

alone and 16 (37.0%) required adjuvant therapy (radiotherapy in 11 patients, suppressive drug therapy in 8 and adrenalectomy in 1) ($p < 0.001$).

Headache was present in 25 patients (41,5%) with dural invasion (CS and sellar floor) and in 24 (56.0%) patients with non-invasive tumors (not statistically significant).

All the CS in which the medial venous compartment was visualized or there was normal pituitary gland interposed between the tumor and the CS were not invaded by the lesion (PPV, 100.0%) ($p < 0.001$).

None of the patients with parasellar extension grade 0 had CSI. On the other hand, all patients with parasellar extension grade 4 had CSI (PPV.100%). The summary of the results regarding parasellar extension can be seen in Table 1.

Displacement of the intracavernous ICA, bulging of the CS lateral wall and an increase in size of the CS were found to be associated with invasion ($p < 0.001$), although only CS lateral wall bulging demonstrated a good PPV (92.3%).

The medial venous compartment was not depicted in all invaded CS (100.0% sensitivity and NPV, $p < 0.001$) and in 54 CS without invasion. This compartment was depicted in the remaining 101 CS without invasion. Non-visualization of the inferior and lateral venous compartments had the highest positive predictive values (92.8% and 100.0%, respectively; $p < 0.001$). The results regarding visualization of the different CS venous compartments are summarized in Table 2.

Table 1. MR-defined parasellar extension correlated with CSI. ($p < 0.001$).

MR parasellar Extension (grade)	Surgical finding (n° of CS)		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Invasion	No invasion				
Crossing of medial intercarotid line? (≥ 1)						
Yes	51	50	100	67.7	50.4	100
No	0	105				
Crossing of median intercarotid line? (≥ 2)						
Yes	33	9	64.7	94.1	78.5	89.0
No	18	146				
Crossing of lateral intercarotid line? (≥ 3)						
Yes	25	1	49.0	99.4	96.1	85.5
No	26	154				
Total encasement of intracavernous ICA? (4)						
Yes	7	0	13.7	100	100	77.8
No	44	155				

Table 2. Sensitivity, specificity, PPV and NPV of MR findings regarding the different CS venous compartments.

Venous compartment not visualized	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Medial	100	65.0	48.5	100
Superior	76.5	94.8	83.0	92.4
Inferior	51.0	98.7	92.8	86.0
Lateral	45.0	100	100	84.7

The CS was always invaded when 3 or more venous compartments were not visualized (PPV 100%, $p < 0.001$).

CS was never invaded when the percentage of encasement of the ICA was lower than 25% (NPV 100%, $p < 0.001$). On the other hand, when more than 45% of the circumference of the intracavernous ICA was involved by the adenoma, all CS were invaded (PPV 100%, $p < 0.001$) (Table 3).

The criteria with stronger association with CSI by χ^2 testing were: a) increase of CS size, b) bulging of CS lateral wall, c) displacement of the intracavernous ICA, d) parasellar extension grade 2 or more, e) non depiction of the superior or inferior venous compartment, f) 2 or more venous compartment not visualized and g) ICA encasement $\geq 30\%$. Comparing all these criteria together, only 3 were statistically significant alone: 2 or more venous compartment not visualized, non depiction of the inferior venous compartment and ICA encasement $\geq 30\%$ (Table 4).

For each of these 3 selected criteria a value weighted by its significance were chosen to make the predictive score of CSI (Table 5). This predictive score ranged from 0 to 6. A total score greater than 2 had the best diagnostic value for CSI (sensitivity 94.1%, specificity 92.9%).

DISCUSSION

The presence of CSI by PA is clinically relevant. Surgical procedures might be more difficult and tumor resection is usually partial in patients with invasive tumors. This yields poorer endocrinological results and adjuvant treatment (radiotherapy, medical suppressive drugs or adrenalectomy) is often necessary. Only 18.0% of the patients in our series with CS and sellar floor dural invasion have been cured by surgery alone. Radiotherapy was performed in 67.0% of the patients with invasive adenomas and drug therapy in 43.5%. The surgical resection was complete in 85.5% of the patients with non-invasive tumors. Sixty-three percent of them have been cured by surgery alone; 25.5% of the patients needed radiotherapy and 18.5% drug therapy. Although preoperative diagnosis of CSI has a major impact on surgical outcome, only a few papers have specifically discussed the issue.

The absence of a bony interface in the lateral limits of the

Table 3. Sensitivity, specificity, PPV and NPV for CSI according to the amount of ICA encasement.

% of ICA encasement	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 10	65.0	48.5	100	
≥ 20	75.5	57.3	100	
≥ 25	83.2	66.2	100	
≥ 30	93.5	82.5	97.3	
≥ 35	96.1	86.3	92.0	
≥ 40	99.3	96.7	88.0	
≥ 45	100	100	86.5	
≥ 50	100	100	85.6	
≥ 60	100	100	84.6	
≥ 70	100	100	84.2	
≥ 80	100	100	80.3	
≥ 90	100	100	78.2	

pituitary fossa might explain why tumor extension to the parasellar region and invasion of the CS are relatively common. A dural bag limited laterally by venous spaces within the CS surrounds the pituitary gland. There is only a thin dural layer between the gland and CS, which is called the medial wall. In about 30% of normal individuals, the pituitary gland has a lateral expansion reaching the intracavernous ICA, but the encasement of the ICA by the gland is always less than 25%⁸. Laterally invading tumors have to be distinguished from these lateral normal pituitary expansions.

Intraoperative findings were considered the gold standard for CSI in our study. This is possibly the best single objective available criterion, but it is highly dependent on the surgeon's personal experience and it has to be recognized that in some patients it is very difficult to adequately visualize the lateral aspects of the pituitary fossa.

Table 4. Odds ratio and significance of the criteria selected by the forward stepwise analysis.

Criteria	Significance	Odds ratio
Inferior venous compartment not visualized	P<0.011	18.5
2 or more venous compartment not visualized	P<0.089	4.0
ICA encasement \geq 30%	P<0.001	49.2

Table 5. Score values of each significant criteria.

Criteria	No	Yes
Inferior venous compartment not visualized	0	2
2 or more venous compartment not visualized	0	1
ICA encasement \geq 30%	0	3

MRI is superior to CT scanning in defining the pituitary gland and the sellar region and its boundaries. On the other hand, both techniques do not adequately depict the medial wall of the CS^{4,9-13}.

The prevalence of CSI in our series is probably overestimated (46.5% of the patients). The present series did not include all the patients with PA treated at our institution. Intervening patients were excluded due to non-availability of adequate MRI images for analysis, lack of full clinical or follow-up data or lack of unequivocal intraoperative information regarding invasion or not by the tumor. CSI occurs more often unilaterally. In Scotti et al.⁴ and Cottier et al.² series, invasion by PA occurred only unilaterally. In our series, unilateral invasion by PA was observed in 93.7% of the patients and bilateral invasion occurred in 3 patients (all with GH-secreting adenoma). Knosp et al.¹ observed bilateral invasion in 3 patients from their series (all with nonfunctioning PA).

We observed a significantly increased prevalence of invasion in macroadenomas (83.5% of the patients with invasive tumors). This higher prevalence of invasive tumors has also been observed by others^{1-3,5}, although Scotti et al.⁴ have not noticed such difference. Knosp et al.¹ have also noted that the grade of parasellar extension was directly related to the tumor's size. Selman et al.¹⁴ have demonstrated histologically that dural invasion in adenoma was well correlated to the tumor's size.

Headache is a frequent symptom in PA, but its pathogenesis is not well understood. Arafah et al.¹⁵ observed that patients with PA and headache had increased intrasellar pressure compared to those without headache. In our series, we found no correlation between the presence of dural invasion by the tumor and headache.

We were able to define 4 MR criteria for the absence of CSI in patients with PA: 1- normal pituitary gland interposed

between the tumor and the CS; 2-intact CS medial venous compartment; 3- tumor not crossing the medial intercarotid line and 4- percentage of ICA encasement by the lesion lower than 25%.

Cottier et al.² also considered the presence of normal pituitary gland interposed between the tumor and the CS and intact CS medial venous compartment as seen on MRI as criteria for absence of CSI. Moreau et al.⁵ also observed that there was no actual tumor invasion when the lesion did not cross the medial intercarotid line. Despite high specificity (100,0%), the 3 criteria above for absence of CSI had a very low sensitivity. ICA encasement lower than 25% disclosed the highest specificity (100,0%) and sensitivity (83,0%) for absence of CSI.

Other criteria highly suggestive of absence of CSI in our study were intact superior venous compartment (NPV, 92.4%) and the visualization of at least 3 CS venous compartments (NPV, 96%). Cottier et al.² noted that besides the visualization of an intact CS superior venous compartment, the absence of size asymmetry between the 2 CS, absence of bulging of lateral wall of CS and grade 2 or less of parasellar extension were also good signs of absence of CSI. In the study of Moreau et al.⁵, the signs highly suggestive of absence of invasion were lack of size asymmetry, lack of bulging of the lateral wall of the CS, visualization of at least two venous compartments and non-displaced ICA.

The displacement of ICA and CS size asymmetry were shown to be criteria with good specificity but low sensitivity and PPV for CSI in our series. Cottier et al.² obtained similar results for these criteria.

Bulging of the lateral wall of the CS had a good specificity and PPV but low sensitivity in our series. These findings were in disagreement with Cottier's et al.² data which disclosed a very low PPV.

In our study, we observed that in patients with Knosp parasellar extension grade 3 the CS was probably invaded (VPP, 96.1%) and with grade 4 (total ICA encasement), it was certainly invaded. However, the sensitivity for these criteria was very low. Cottier et al.² and Moreau et al.⁵ also observed that CSI was very likely when the lateral intercarotid line was crossed by the tumor. However, Knosp et al.¹ noted that adenoma with grade 2 or higher always had CSI. Their series evaluated only patients with CSI.

The non-visualization of the inferior or lateral CS venous compartments was very suggestive of CSI (PPV, 92.8% and 100% respectively). CSI was always present when 3 or more CS venous compartments were not depicted on MRI (PPV, 100%). Cottier et al.² further divided the CS inferior venous compartment into carotid sulcus and inferolateral compartments, and observed that non-visualization of the carotid sulcus venous compartment had a high PPV (95.0%) for CSI. However, contrary to our results, these authors did not observe good PPV for invasion when the CS lateral venous compartment was not seen.

Total encasement of ICA by adenoma (grade 4 of Knosp¹) definitely indicated CSI (PPV and specificity of 100%) in our series, but it had low sensitivity and occurred late in time. In our series, only 13.7% of the CSI showed total encasement of ICA. Knosp et al.¹ observed this sign in 32.0% of the invaded CS and Cottier et al.² in 24.0%.

Adenoma grows progressively around the ICA after infiltrating the CS medial wall. Moreau et al.⁵ observed that in patients in whom there was 25% or more of ICA encasement by the tumor CSI was very likely. In our study, we observed that ICA encasement higher than 45% was always associated with CSI (PPV, 100%). Cottier et al.² suggested that at least 67% of ICA encasement would be needed to assure CSI.

Comparing statistically the significant criteria all together, only 3 had separately association with CSI: 2 or more venous compartment not visualized, non depiction of the inferior venous compartment and ICA encasement $\geq 30\%$. With these criteria, we proposed a practical predictive score for CSI to make its preoperative diagnosis easier.

CONCLUSION

Our data showed that accurate analysis of MR findings is useful in the preoperative diagnosis of CSI by PA and is able to generate relevant information regarding the microsurgical outcome in this patient's population. The most specific and precocious sign of invasion was the encasement of the intracavernous ICA greater than 45%; when ICA encasement was lower than 25% the CS was never invaded. CS was definitely invaded when the lateral venous compartment was not visualized or when three or more venous compartments were not depicted. CS was never invaded when the medial venous

compartment was intact or normal pituitary gland was interposed between the adenoma and the CS.

The most useful sign to predict CSI was the encasement of ICA greater than 30%. This precocious finding had the best sensitivity (92.1%), specificity (93.5%) and PPV (82.5%).

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