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ARTICLE

Pituitary macroadenoma: analysis of intercarotid artery distance compared to controls

Macroadenoma de hipófise: análise da distância intercarotídea comparada a controles

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ABSTRACT

Objective: To evaluate the intercarotid distance (ICD) of patients with pituitary macroadenoma and compare to heatlhy controls. **Method:** We retrospectively reviewed contrast-enhanced MRI images from twenty consecutive patients diagnosed with non-functioning pituitary macroadenoma, measured the ICD at two different levels (petrous segment – ICD1 and horizontal cavernous segment – ICD2) and compared to twenty paired controls. **Results:** There was no statistically significant difference of the mean ICD1 between the groups and subgroups. For the ICD2 there was statistically significant difference between the case and controls. However, there was no significant difference between the patients with smaller adenomas and the controls. In contrast, the patients with giant adenomas showed statistically significantly higher ICD2 than the controls. **Conclusion:** The ICD at the horizontal segment of the cavernous carotid tends to be wider in patients with giant pituitary adenomas than in healthy individuals or patients with smaller adenomas.

Keywords: Pituitary gland; pituitary disease; internal carotid artery; endoscopy; sella turcica.

RESUMO

Objetivo: Avaliar a distância intercarotídea (DIC) de pacientes com macroadenoma de hipófise e comparar com controles saudáveis. **Método:** Foram analisados retrospectivamente imagens de ressonância magnética com contraste de vinte pacientes consecutivos com diagnóstico de macroadenoma hipofisário não-funcionante, medidas as DIC em dois níveis diferentes (segmento petroso – DIC1 e segmento cavernoso horizontal – DIC2) e comparados com vinte controles pareados. **Resultados:** Não houve diferença estatisticamente significativa da DIC1 média entre os grupos e subgrupos. Para a DIC2 houve diferença estatisticamente significativa entre os casos e controles. No entanto, não houve diferença significativa entre os doentes com adenomas menores e os controles. Entretanto, os pacientes com adenomas gigantes tiveram estatisticamente significativamente DIC2 que os controlos. **Conclusão:** A DIC no segmento horizontal da carótida cavernoso, tende a ser mais larga em doentes com adenomas hipofisários gigantes do que em indivíduos saudáveis ou de pacientes com adenomas menores.

Palavras-chave: hipófise; doenças da hipófise; artéria carótida interna; endoscopia; sela túrcica.

Despite all the improvement in transsphenoidal surgery, the anatomical knowledge has been a main issue stressed by most authors[1]. In the transsphenoidal approach for pituitary adenomas, detailed preoperative planning with information regarding the sphenoid sinus, tumoral involvement of adjacent structures (cavernous sinus, suprasellar region, carotid arteries) and intercarotid distance (ICD) is critical. Despite that, there is little literature regarding the ICD at the parassellar region of the intracranial carotid arteries at its cavernous segment and its modifications due to the sellar pathologies, specially non-functioning pituitary adenomas[2,3,4,5,6].

Although vascular injuries have become less frequent over the years, with reports ranging from 0–3.8%[7,8,9,10,11,12,13,14,15,16,17,18,19,20], it is still considered one of the most important complications in the transsphenoidal approaches due to its potential hazardous effects and difficult management. Taking this into consideration, it is crucial that every surgeon knows exactly the carotid artery position and its relation to the lesion.

This study has the aim to measure and analyze ICD in a series of patients with non-functioning pituitary adenomas with no previous treatment and correlate the data with measurements in controls with no endocrinological, sellar or parassellar disease.

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METHOD

We retrospectively reviewed twenty consecutive patients diagnosed with non-functioning pituitary macroadenoma (>10 mm in any plane) whom underwent first time endonasal endoscopic transsphenoidal resection assisted by neuronavigation from January 2008 to December 2010. This group was further sub-classified in adenoma and giant adenoma, defined as lesions with more than 40 mm in any plane. The controls (n = 20) were age and sex matched with the cases and had no endocrinological, sellar or parassellar disease. Age matching was not perfect, maximum age difference was 5 years and the mean difference 1,9 years.

Fine cut (1 mm) T1W gadolinium enhanced MRI imaging were acquired using a 1.5-T MR imaging unit (Signa®; General Electric Medical Systems). All the imaging data was uploaded to the BrainLab Neuronavigation Workstation (BrainLab iPlan® Cranial 2.6 software) database and analyzed in axial, coronal and sagittal planes for the following parameters:

- Intercarotid distance, defined as the smallest distance between the inner walls of the carotid artery lumen enhanced by gadolinium, was measured at two levels:
  - intercarotid distance 1 (ICD1) – petrous carotid segment after the cranial bend (Figure 1, A and B);
  - intercarotid distance 2 (ICD2) – cavernous carotid segment at the mid portion of its horizontal part (Figure 1, C and D).

The cases group was further analyzed regarding the tumor dimensions as following (Figure 2, Table 1):

- largest anteroposterior dimension in axial plane MRI;
- largest latero-lateral dimension in coronal plane MRI;
- largest craniocaudal dimension in sagital plane MRI.

All patients in the cases group were further classified according to (Table 1):

- Cavernous sinus invasion (CSI): defined as Knosp grade 3 or 4 on any side[21];
- Sphenoid sinus invasion (SSI): defined as presence of tumor inside the sphenoid sinus on MRI.

The measurements were performed by two different and independent observers following the same protocol: first, 5 stage zoom was applied and then all measurements where performed and recorded in millimeters with one decimal unit precision. The mean value of the results found by the two observers for each measurement were used for the statistical analysis (Table 2).

Statistical methods

Statistical analysis was performed with Medcalc statistics software (MedCalc version 13.1.2, Ostend, Belgium). For the inter-observer reproducibility analysis we used

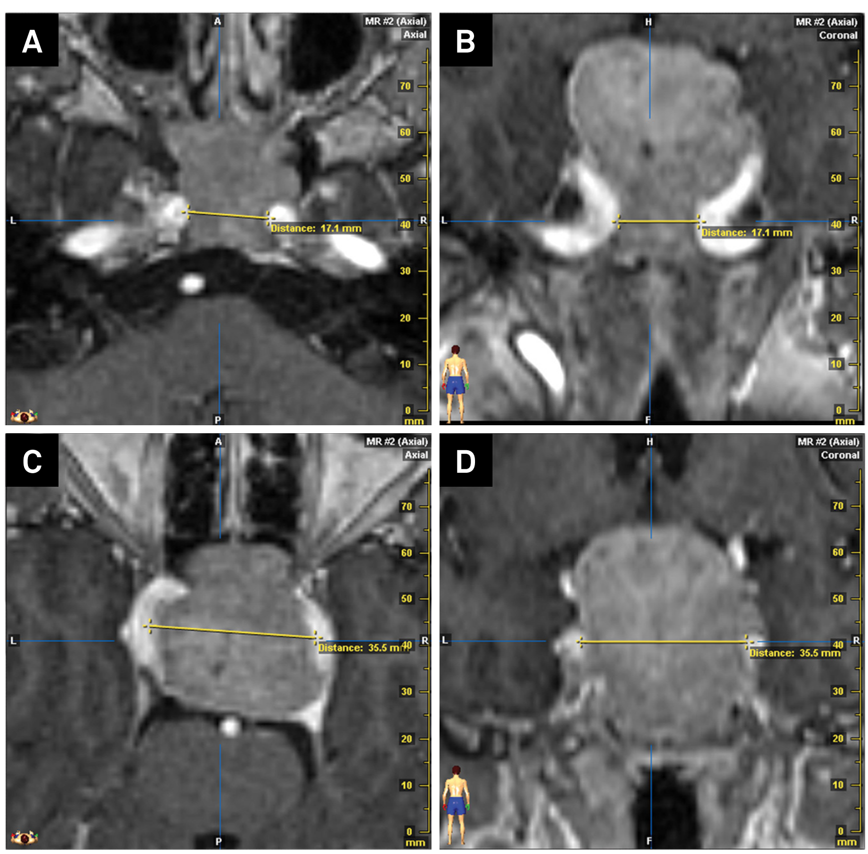

Figure 1. T1-weighted MRI of the sellar and parasellar regions in a patient with pituitary adenoma. (A) and (B) intercarotid distance 1 (ICD1) measured in axial and coronal plane. (C) and (D) intercarotid distance 2 (ICD2) measured in axial and coronal plane.

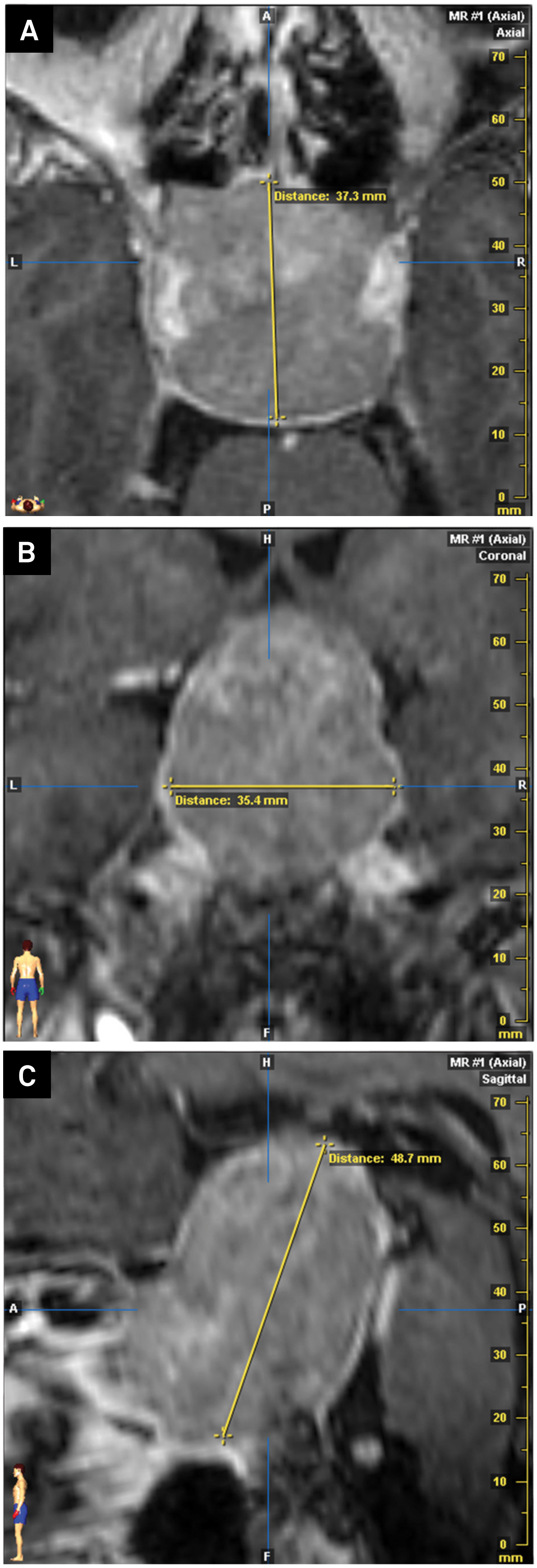

Figure 2. T1-weighted gadolinium enhanced MRI of the sellar and parasellar regions in a patient with pituitary adenoma. (A) anteroposterior, (B) latero-lateral and (C) craniocaudal measurements of the tumor.

the intraclass correlation coefficient. The mean values of continuous variables in 2 groups were compared with the 2-sample t test if the variances did not differ significantly ($p > 0.05$). For significantly different variances, we used the Welch test (reported in the results). Normally distributed data are summarized by mean ± standard deviation. We calculated the Pearson correlation coefficient for the assessment of associations between continuous variables. We used Fisher's exact test to asses the relation between categorical variables. Statistical significance was defined as a probability value < 0.05 (Table 3).

RESULTS

The mean age in the cases group was 52,3 years (range, 21–78 years) and in the control group was 52,3 years (range, 21–83 years) and they did not differ significantly ($p = 0.8693$). The sex match was perfect and there were 9 males and 11 females in each group, cases and controls. Sex proportion at adenoma subgroup (6M:7F) and giant subgroup (5M:2F) did not differ significantly ($p = 0{,}3742$; according to Fisher's exact test).

There was an excellent correlation between the two observer measurements of the ICD1, ICD2 and tumor dimensions, as shown by the Interclass Correlation Coefficient (ICC) equals to 0.93, 0.91 and 0.99, respectively (Figure 3). This data indicates that the method of measurement used in the study has an excellent reproducibility to evaluate the intercarotid distance when performed by two independent observers.

The mean ICD1 in the cases group was 21,17 ± 2,49 mm and in the controls group was 19,89 ± 2,65 mm and there was no statistically significant difference between the two groups ($p = 0.1239$). In the adenoma subgroup the mean ICD1 was 21,26 ± 2,48 mm and in the giant subgroup the mean was 21.00 ± 2.69 mm. There were no statistically significant differences between the mean ICD1 values of the adenoma subgroup and the control group ($p = 0.1470$), the giant subgroup and the control group ($p = 0.3513$), neither the adenoma subgroup and the giant subgroup ($p = 0.8296$) (Figure 4, 5).

In the cases group the mean ICD2 was 24.27 ± 5.14 mm and in the control group it was 19.41 ± 3.00 mm and the difference was statistically significant between the two groups ($p = 0.001$ according to the Welch test). In the adenoma subgroup the mean ICD2 was 21.54 ± 3.52 mm and in the giant subgroup it was 25.97 ± 3,63 mm. The ICD2 did not differ significantly among the adenoma subgroup and the controls ($p = 0.0724$). However, there was highly significant difference between the giant subgroup and the control group ($p < 0.0001$), as well as the giant subgroup and the adenoma subgroup ($p = 0.0002$) (Figure 5, 6).

Table 1. Cases group tumor characteristics, sub-classified as adenoma and giant.

Pt.No.	Group	AP*	LL*	CC*	Main Growth	Knosp R	Knosp L	CSI	SSI
1	Adenoma	11,5	14	12,8	LL	0	0	N	N
2	Adenoma	22,8	20,8	29,8	CC	0	1	N	N
3	Adenoma	17,8	15,2	16,4	AP	0	1	N	N
4	Adenoma	18,8	14,3	14,5	AP	4	1	Y	N
5	Adenoma	24,6	22,3	19,9	AP	2	1	N	Y
6	Adenoma	21,3	19	18	AP	0	0	N	Y
7	Adenoma	14,7	14,9	17,7	CC	0	1	N	N
8	Adenoma	20,1	23,4	22,8	LL	3	2	Y	N
9	Adenoma	18,3	25,2	25,7	CC	1	3	Y	N
10	Adenoma	24,5	30,2	26,5	LL	4	3	Y	N
11	Adenoma	14,1	22,1	12,6	LL	0	0	N	N
12	Adenoma	14,8	16,9	22,7	CC	1	2	N	N
13	Adenoma	22,5	23,9	36,3	CC	2	0	N	Y
14	Giant	32,6	30,9	40,1	CC	1	2	N	N
15	Giant	26,7	36,2	49,5	CC	0	0	N	Y
16	Giant	33,7	35,2	47,9	CC	3	2	Y	Y
17	Giant	22,4	25,7	40,6	CC	1	1	N	Y
18	Giant	21	27,4	40,5	CC	1	1	N	Y
19	Giant	22,6	29,8	59	CC	2	1	N	Y
20	Giant	36,4	35,6	49,1	CC	0	1	N	Y

AP: anteroposterior; LL: latero-lateral; CC: craniocaudal; CSI: cavernous sinus invasion; SSI: sphenoid sinus invasion; *measurements in millimeters.

Table 2. Intercarotid distance measurement for all individuals.

Pt.No.	Subgroup	ICD1*	ICD2*	Pt. No.	Subgroup	ICD1*	ICD2*
1	Adenoma	19,6	16,9	21	Control	19,6	21,3
2	Adenoma	21,4	21,9	22	Control	17,5	20,7
3	Adenoma	17,1	21,8	23	Control	20,1	17,8
4	Adenoma	20,8	17,2	24	Control	21,8	12,8
5	Adenoma	22,7	24,6	25	Control	19,8	19,1
6	Adenoma	19	17,2	26	Control	21,6	17,8
7	Adenoma	18,3	18,8	27	Control	21,5	18,9
8	Adenoma	22,1	20,9	28	Control	17,9	20
9	Adenoma	20,2	22,8	29	Control	18,4	18
10	Adenoma	25,3	28,2	30	Control	16,5	19,6
11	Adenoma	25,2	26,6	31	Control	24,3	22,5
12	Adenoma	23,3	21	32	Control	19,9	18
13	Adenoma	21,4	22,2	33	Control	16,4	14,5
14	Giant	25,7	26,8	34	Control	17,9	18,3
15	Giant	20,4	32,5	35	Control	18,1	20,5
16	Giant	16,8	34,5	36	Control	23,5	25
17	Giant	20,2	25,2	37	Control	21,3	21,9
18	Giant	21,3	26,1	38	Control	25	23,9
19	Giant	20,2	28,2	39	Control	15,5	15,8
20	Giant	22,4	32	40	Control	21,2	21,9

ICD1: intercarotid distance 1; ICD2: intercarotid distance 2; Pt. No.: patient number; *measurements in millimeters.

The Pearson correlation coefficient showed no correlation between the ICD1 and any of the tumor dimensions ($p > 0.05$). However, the ICD2 showed excellent correlation with tumor laterolateral size and ICD2 (Pearson $r = 0.9048$; $p < 0.0001$), good correlation with tumor craniocaudal size (Pearson $r = 0.7679$; $p = 0.0001$) and moderate correlation with anteroposterior tumor size (Pearson $r = 0.6985$; $p = 0.0006$) (Figure 7). According to Fisher's exact test there is statistically significant correlation between craniocaudal main growth and the giant subgroup (100%) compared to the adenoma subgroup (38,46%) ($p = 0.0147$).

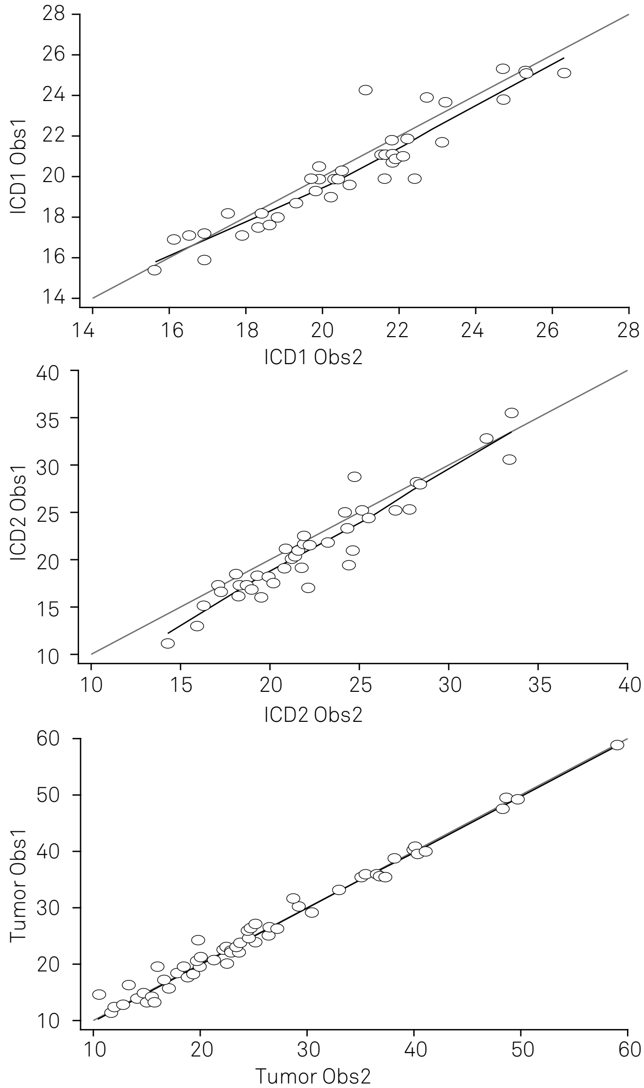

Figure 3. Scatter diagram between the measurements of the two observers for intercarotid distance 1 (ICD1), intercarotid distance 1 (ICD2) and tumor size. Grey line representing the line of equality (x=y). Black line representing the trend line os the scattered data.

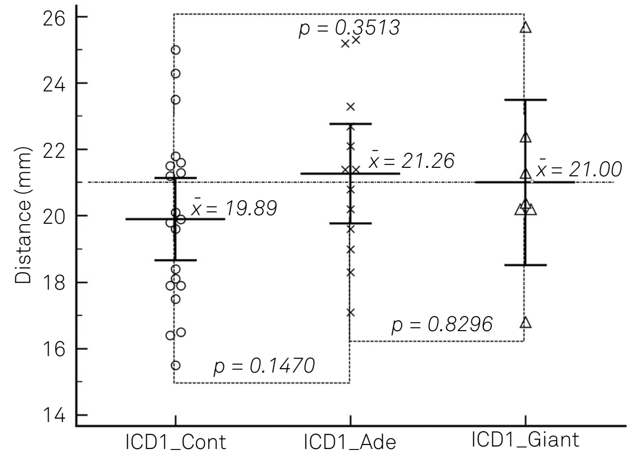

Figure 4. Dot plot graph comparison of intercarotid distance 1 (ICD1) between control group, adenoma subgroup and giant subgroup. Wider horizontal line representing the mean (value in bold), vertical line representing the 95% confidence interval. There is no statistically significant difference between the means.

Table 3. Statistical analysis results.

Variável	Difference of means (95%CI)*	Statistical Test Result	p-value**
ICD1			
Control vs. Cases	1,28 (-0,36–2,92)	1,574***	0,1239
Control vs. Adenoma	1,37 (-0,51–3,25)	1,487***	0,147
Control vs. Giant	1,11 (-1,29–3,51)	0,950***	0,3513
Giant vs. Adenoma	0,26 (-2,25–2,78)	0,218***	0,8296
ICD2			
Control vs. Cases	4,85 (2,13–7,57)	3,642****	0,0010*****
Control vs. Adenoma	2,13 (-0,20–4,47)	1,860***	0,0724
Control vs. Giant	9,91 (7,04–12,77)	7,127***	<0,0001*****
Giant vs. Adenoma	7,78 (4,27–11,28)	4,664***	0,0002*****
Control female vs. male	3,90 (1,77–6,09)	3,759***	0,0014*****

ICD1: intercarotid distance 1; ICD2: intercarotid distance 2; *measurement in millimeters, **statistically significant if p < 0,05, ***t-test, ****Welch test, *****statistically significant value.

In the controls group the mean ICD2 among males was 21.17 ± 2.12 mm (n = 11) and among females was 17.26 ± 2.52 mm (n = 9) and the difference was statistically significant (p = 0.0014) (Figure 8).

No correlation was found, according to the Fisher's exact test, between the occurrence of cavernous sinus invasion and the subgroups, adenoma (30,76%) or giant (14,28%) (p = 0.4058). However, there was a significant correlation between the subgroups, adenoma (23.07%) or giant (85,71%), and the occurrence of sphenoid sinus invasion (p = 0.0166).

DISCUSSION

The intercarotid distance plays a crucial role in transsphenoidal surgery, once it determines the corridor to the sellar and suprassellar spaces and some papers have studied it. Different methods of measuring the intercarotid distance have been used in the literature[1,2,6,17,22,23], among them, the T1W gadolinium enhanced MRI. Although it was not a primary objective in our study, we could conclude that the intercarotid distance measurement using enhanced-MRI is a reproducible method to evaluate the intercarotid distance, with excellent inter-observer correlation (ICC = 0,93 for ICD1; ICC = 0,91 for ICD2).

The narrowest intercarotid distance was found to be either in the suprassellar segment[24] or at the level of the tuberculum sellae[25,26]. The mean values for the intercarotid distance at the selar region in healthy individuals reported in the literature have a wide range, varying from 12 mm to 18 mm[1,3,4,6,22,23,25,27,28,29], what we believe to be related to the method used to measure the distance and the ethnical differences between the study populations. In our study, the mean intercarotid distance at its horizontal portion at the sellar

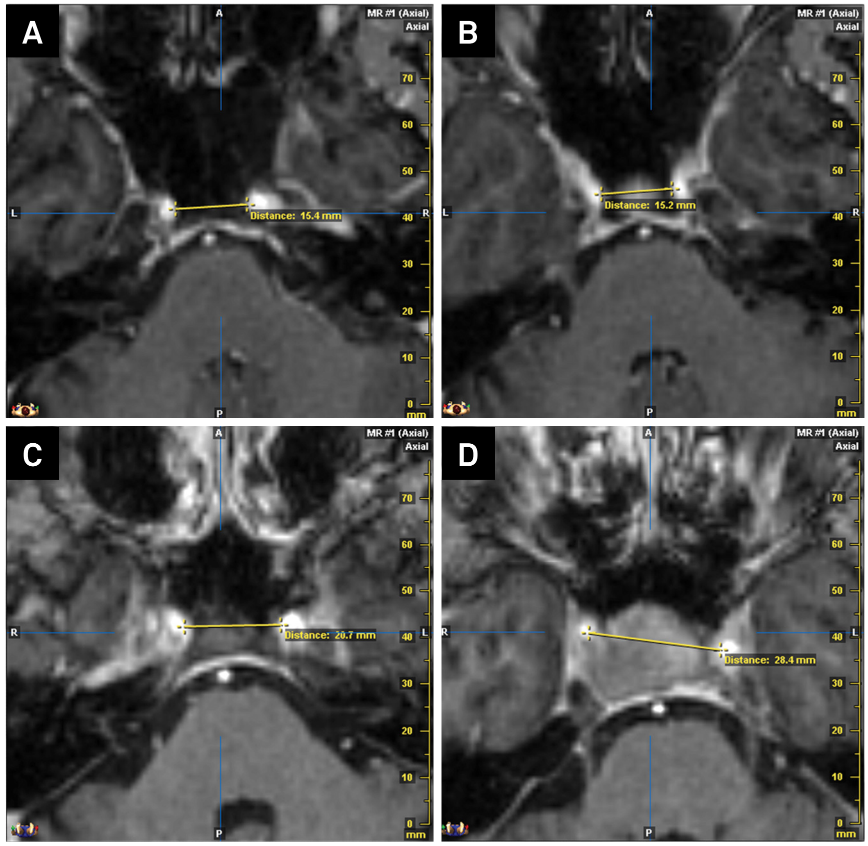

Figure 5. T1-weighted gadolinium enhanced axial MRI of the sellar and parasellar regions comparing the ICDs between the control (left) and its paired patient with adenoma (right). (A) ICD1 and (B) ICD2 of patient 39; (C) intercarotid distance 1 (ICD1) and (D) intercarotid distance 2 (ICD2) of patient 19.

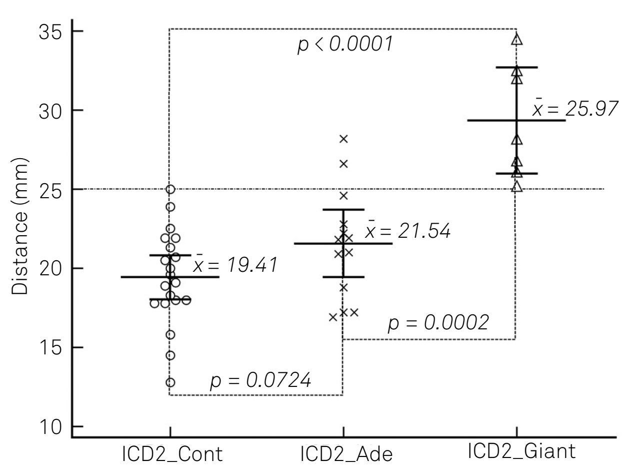

Figure 6. Dot plot graph comparison of ICD2 between control group, adenoma subgroup and giant subgroup. Wider horizontal line representing the mean (value in bold), vertical line representing the 95% confidence interval. There is no statistically significant difference between the controls group and the adenoma subgroup, however, the giant subgroup demonstrates a higher mean than the controls group and the adenoma subgroup.

region (ICD2) in the controls group was 19.41 ± 3.00 mm, a difference probably attributable to the same reasons they differ in another studies. Different from previous reports[23], there was a statistically significant difference between males and females ICD2 in the control group (males = 21.17 mm, females = 17.26 ± 2.52 mm; p = 0.0014).

As we expected there was no statistically significant difference between the groups neither the subgroups related to the ICD1. The petrous segment of the carotid artery has direct contact to bone and thick dural layers that would prevent its displacement and the disease itself is localized to a more cranial extent of the carotid arteries. We used this measurement as a way to assure that the displacement of the carotid arteries at the sellar region is not related to any other influence than the tumor growth.

In patients with selar and parassellar pathology a few papers have studied the differences in the intercarotid distance compared to healthy individuals. Ebner et al have demonstrated that in acromegalic patients the mean intercarotid distance is narrower than in healthy individuals (1.64 ± 0.40 cm vs 1.90 ± 0.26 cm)[30]. Several studies have showed that patients with pituitary adenomas have higher intercarotid distance than individuals with no sellar pathology, and patients with bigger lesions tend to have bigger intercarotid distances than patients with smaller lesions (less than 10mm)[2,4,6,21]. Our results support the previous reports, showing a bigger ICD2 in the cases group. In the subgroup analysis, there was no significant difference between the controls and the

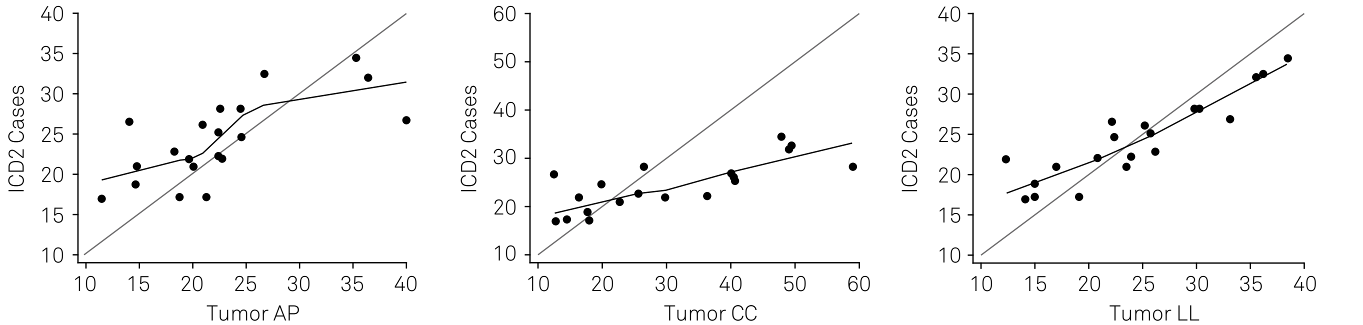

Figure 7. Scatter diagram between the anteroposterior (AP), craniocaudal (CC) and latero-lateral (LL) dimensions related to the intercarotid distance 2 (ICD2), showing a better concordance between the intercarotid distance 2 (ICD2) and the latero-lateral dimension.

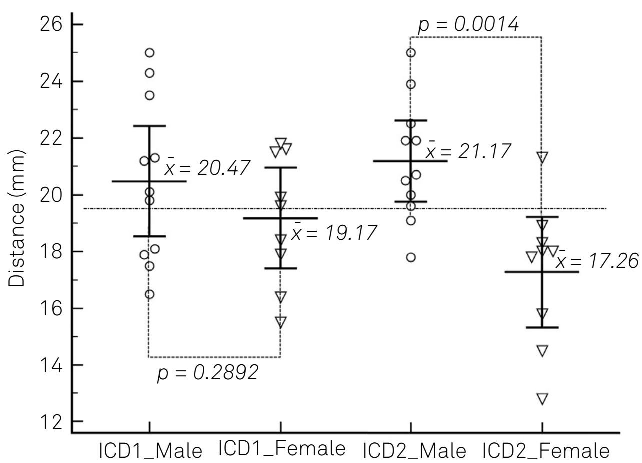

Figure 8. Dot plot graph comparison of intercarotid distance 1 (ICD1) and intercarotid distance 2 (ICD2) between males and females of the control groups. Wider horizontal line representing the mean (value in bold), vertical line representing the 95% confidence interval. The graph demonstrates statistically significant difference between males and females for ICD2, but not for ICD1.

patients with non-giant adenomas. However, the difference between the giant subgroup and both, the adenoma subgroup and the controls, were statistically significant. We believe this difference is probably related to the intrinsic anatomy of the sella and its surrounding structures. Cranial extent of the tumor is achieved by either expansion of the diaphragma sellae, a very complacent structure, or the disruption of it which explains the fact that craniocaudal dimension is usually the biggest one in giant adenomas (Table 2). Once the tumor has grown cranially it might be subjected to resistance of the distressed diaphragma sellae and the brain tissue causing pressure downwards that could direct the growth of the tumor to lateral, once the cavernous sinus might be structurally less resistant to pressure than the sellar bony walls. In this particular region the carotid artery is relatively free of dural attachments and bone surroundings and thus would be displaced more prominently.

Scotti et al.[4] in their series of 74 patients, 24 of whom with pituitary adenomas, demonstrated that in patients with adenomas and no evidence of cavernous sinus invasion the carotid arteries tend to be more displaced than in those with signs of cavernous sinus invasion. In another report Sasagawa et al compared the ICD at the cavernous carotid pre and postoperatively and demonstrated that in invasive pituitary adenomas the ICD tends to be reduced after surgery, probably because of disruption of supportive tissues that keep the carotid artery in place at this segment[5]. In contrast, in our study, the amount of patients with radiological signs of CSI did not differ between the adenoma and the giant subgroup, although the ICD2 was significantly higher in the giant subgroup. Thus, we conclude that the CSI had no influence in the ICD in our series.

Despite its importance, the ICD has still limited literature regarding its modification due to pathological processes. Our results reinforce the logically increase in the ICD with large pituitary tumors[2,4,6,21], however we could not relate it to CSI as other authors did[4,5]. Interestingly, there was no statistical difference in the ICD2 when we compared the adenoma with the control group, but the ICD2 it was significantly higher in the giant subgroup when we compared to both, adenomas subgroup and control group (Figure 6). This finding might be related to the sample characteristics, anyhow we believe there may be anatomical features that are disrupted by the tumor pressure against the carotid arteries at a certain point that would permit a higher carotid displacement. Bearing this idea, the tumor consistency and growth rate may play a role in the way the carotid arteries are displaced by the tumor. Further studies are needed to both prove our theories and understand the direct and indirect anatomical changes caused by pituitary adenomas to the sellar and parasellar structures.

In this study, we decided not to evaluate the extent of tumor resection for several reasons. There are multiple factors that may affect the extent of resection, for example, tumor size, cavernous sinus invasion and consistency of the tumor. Our sample is not big enough for multivariate analysis to exclude the other factors and evaluate only the ICD. Moreover, we did not have any case of abnormally little ICD that would hinder the resection or obstruct the approach to the sellar space. Sasagawa et al.[5], were the only relating grade of resection with ICD. In their study gross total or subtotal resection was less achieved in patients with ICD lower than 25 mm, however, the aforementioned distance is still higher than the mean ICD found in ours and other studies, so we do not recommend that measurement as an obstacle to tumor resection[1,3,4,5,6,22,23,25,27,28,29].

In conclusion, apparently the ICD at the horizontal segment of the cavernous carotid tends to be wider in patients with giant pituitary adenomas. Differently from other reports we found no relation between cavernous sinus invasion and the ICD. In our controls, the males had a significantly wider ICD than the females, which is not found in any other studies and could represent an ethnic difference.

We believe the study of the carotid arteries anatomy in sick and healthy individuals is essential to the skull base surgery, specially for endoscopic endonasal approaches that use the intercarotid corridor for most of its approaches. Our study is limited by the sample size and its retrospective nature and further research has to be carried to confirm our data and validate it for other populations.

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