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*Neuroanatomical Study*

# Microsurgical anatomy of the lateral walls of the pituitary fossa

**S. Peker**[1], **O. Kurtkaya-Yapıcıer**[2], **T. Kılıç**[1], and **M. N. Pamir**[1]

[1] Marmara University Department of Neurosurgery, Neurological Sciences Institute, Istanbul, Turkey
[2] Marmara University Department of Pathology, Neurological Sciences Institute, Istanbul, Turkey

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## Summary

*Background*. The aim was to evaluate the microanatomy of the lateral wall of the pituitary fossa in cadavers.

*Methods*. Histological sections of sellar-parasellar specimens from 13 cadaver heads were examined. The thickness of the pituitary capsule and inferior and lateral walls of the pituitary fossa were measured, and the collagenous structure of these layers was evaluated.

*Findings*. The pituitary gland is enveloped by a tough, thin, fibrous capsule. The inferior wall of the pituitary fossa is composed of relatively thick dura (mean thickness in the 13 specimens, 171 μm). Each lateral wall of the fossa has a thin layer of dura (mean thickness in the specimens, 85 μm). The pituitary capsule and the dural layers in the lateral and inferior walls of the fossa were immunopositive for collagen types I and II. Collagen types III, IV and V were detected only in the pituitary capsule.

*Conclusions*. Weakness of the lateral walls of the pituitary fossa and the degree to which collagen fibres in the pituitary capsule have been biochemically damaged are important factors in infiltration of the cavernous sinus by a pituitary adenoma.

*Keywords:* Anatomy; cavernous sinus; collagen; pituitary adenoma; pituitary gland; sella.

Most pituitary adenomas do not extend to the vital structures adjacent to the sella, such as the cavernous sinus. The majority of these tumours can be treated successfully by surgery. Unfortunately, however, 10–20% of pituitary adenomas do infiltrate the cavernous sinus, and such lesions must be treated with adjuvant therapies [1, 11, 16, 21].

The reasons why some of these tumours progress to involve the cavernous sinus are still unclear. Two major theories have been proposed in the literature. Some authors contend that pituitary adenomas are biologically benign, and that parasellar infiltration is due to weakness or fenestrations in the lateral wall of the pituitary fossa [8, 9, 35]. Others have postulated that the structure of the lateral walls of the pituitary fossa is not the issue, and that the biological behaviour of the tumour is the main factor in infiltration [31]. Numerous studies have investigated the anatomy of the sellar and parasellar regions [2, 14, 19, 22, 24, 25, 29]; however, relatively few reports have focused on the anatomy of the walls of the cavity which contains the pituitary gland [3, 4, 6, 7, 15, 34]. The aim of this study was to evaluate the microsurgical anatomy of the lateral walls of the pituitary fossa in adult human cadavers, and to compare the findings with those in the literature.

## Materials and methods

All work was conducted in the Microsurgical Anatomy Laboratory of the Marmara University Neurological Sciences Institute. Thirteen human adult cadaver heads were used for the study. For each cadaver head, initially all blood and clots were flushed from the vessels and the tissues were fixed in 10% formalin solution. The arteries and veins were then injected with coloured latex. The sellar-parasellar regions were removed from each head *en bloc*, and the bone in each specimen was decalcified. From 12 of the 13 specimens, we obtained five 5 μm-thick coronal sections for histological study. All these sections were routinely stained with hematoxylin-eosin and Masson's trichrome stains. For the thirteenth cadaver, we removed the pituitary gland from the pituitary fossa using microsurgical techniques, and then examined the macro-anatomical and histological structure of the fossa walls.

On the slides of the above-mentioned 12 specimens, the thickness of the pituitary capsule and the thicknesses of the dural layers which composed the inferior wall and the two lateral walls of the pituitary fossa were measured (three measurements in total per section) using an ocular micrometer. Observations were made at ×200 magnification, where the length between two gridlines on the micrometer is 5 μm. For each specimen, the thicknesses were measured in all five slides and the means for each of the four structures were recorded. The histomorphological features and staining characteristics of the fibrous tissues in the region of the pituitary (indicating collagen types present) were also evaluated.

*Collagen immunohistochemistry*

From each of the 12 sellar-parasellar specimens, we also cut five 5 µm-thick sections for immunohistochemical study of collagen content. Each section was placed on a slide coated with 3-aminopropyletxylene and deparaffinized at 37 °C for 12 hrs. The slides were then submersed in xylene for three 5-min periods, and in 96% alcohol for three 10-min periods. Endogenous peroxidase activity was stopped by immersion in 3% hydrogen peroxide in methanol for 30 min.

*Staining for collagen types I, II, III, IV and V*: The sellar and parasellar regions of the 12 human cadaver specimens were assessed for collagen types in order to gain information about the nature of the structures near the pituitary gland. The sections were rehydrated, and the presence of collagen type II antigen was assessed after protein digestion in pepsin for 15 min at 37 °C. For collagen types III and IV, antigen retrieval was carried out in 10% citrate buffer. Antigen retrieval was not carried out for collagen types I and V. Slides were incubated with the different primary antibodies at room temperature for specific periods, as follows: 30 min for collagen type I (DAKO Corp., Carpinteria, CA, USA; diluted 1:50); 2 hrs for collagen type II (clone 2B1.5, Neomarkers, CA, USA); 1 hr for collagen type III (clone collag III, Innovex Biosciences, CA, USA; diluted 1:30); 2 hrs for collagen type IV (clone PHM-12 + CIV22, Neomarkers, CA, USA), and 2 hrs for collagen type V (Human collagen type V, Innovex Biosciences, CA, USA; diluted 1:20). Staining was then done using the avidin-biotin peroxidase complex (ABC) method. Diaminobenzidine served as the chromagen, and hematoxylin was applied for counterstaining. Appropriate positive and negative controls were used.

## Results

The micro-anatomy findings and collagen types detected in the coronal sections from the 12 sellar-parasellar specimens were as follows:

### *Micro- and macroanatomical structure*

The pituitary gland was observed lying in the pituitary fossa. The gland was found to be covered by two distinct structures: capsule and dura. In all specimens, the pituitary capsule was composed of dense fibrous tissue and was tightly fixed to the gland. The thickness of the capsule ranged from 10–60 µm (mean 39 µm, median 40 µm). The inferior wall of the pituitary fossa was composed of a thick layer of dura mater that ranged from 55–450 µm in

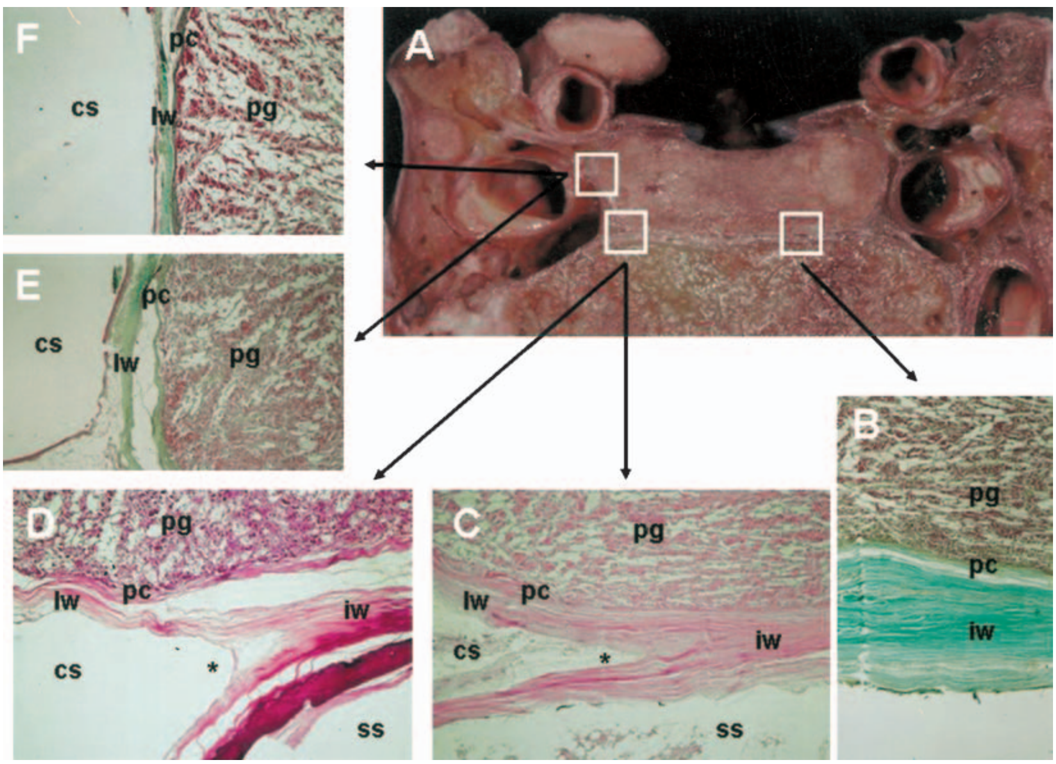


Fig. 1. A macroscopic view of one of the sellar-parasellar specimens (right upper) (A) with insets showing microscopic views; The inferior wall (*iw*) of the pituitary fossa is a thick layer of dura distinct from the pituitary capsule (*pc*) (B); At the inferolateral edges of the fossa, the inferior wall divides (*) in two to form a Y (C, D). One arm of the Y continues as the sphenoidal part of the medial wall of the cavernous sinus, and the other turns superiorly to form the lateral wall (*lw*) of the fossa. Note the clear distinction between the pituitary capsule and the lateral wall (E, F). cs, cavernous sinus; pg, pituitary gland; ss, sphenoid sinus. B, E and F, Masson's trichrome; original magnification, ×40. C and D, hematoxylin and eosin; original magnification, ×40

thickness (mean 171 μm, median 180 μm). The fibres in this dural layer were oriented horizontally. At each of the inferolateral edges of the pituitary fossa, the thick dura of the inferior wall split into two thinner layers that formed a Y shape. One of the arms of the Y continued as the sphenoidal part of the medial wall of the cavernous sinus, and extended to the lateral limit of the sinus. The other arm of the Y, which formed the sellar part of the medial wall of the cavernous sinus (lateral wall of the pituitary fossa) was directed superiorly. This wall ranged from 10–180 μm in thickness (mean 85 μm, median 70 μm) and was clearly much thinner than the inferior wall of the fossa (Fig. 1).

In 2 (17%) of the 12 specimens, the lateral walls of the fossa were extremely thin (mean and median thicknesses for the measurements in the multiple sections, 10 μm and 15 μm, respectively). In two other specimens (17%), the thicknesses of the dura in the left and right lateral walls of the fossa differed greatly (140 μm and 10 μm, respectively, for one specimen; 120 μm and 45 μm, respectively, for the other specimen).

As described above, in the thirteenth sellar-parasellar specimen the pituitary gland was surgically removed from the fossa and the macro-anatomy was examined. The gland was enclosed in a tough sac that appeared to be a single layer of dura. The sac was distinct from the pituitary capsule. These findings were consistent with the histopathological observations in the other specimens. The anterior and inferior walls of the fossa appeared to be smooth and clean dura. In contrast, the lateral walls appeared to be composed of dura and fibroadipose tissue combined (Fig. 2a, b). The neurohypophysis was observed

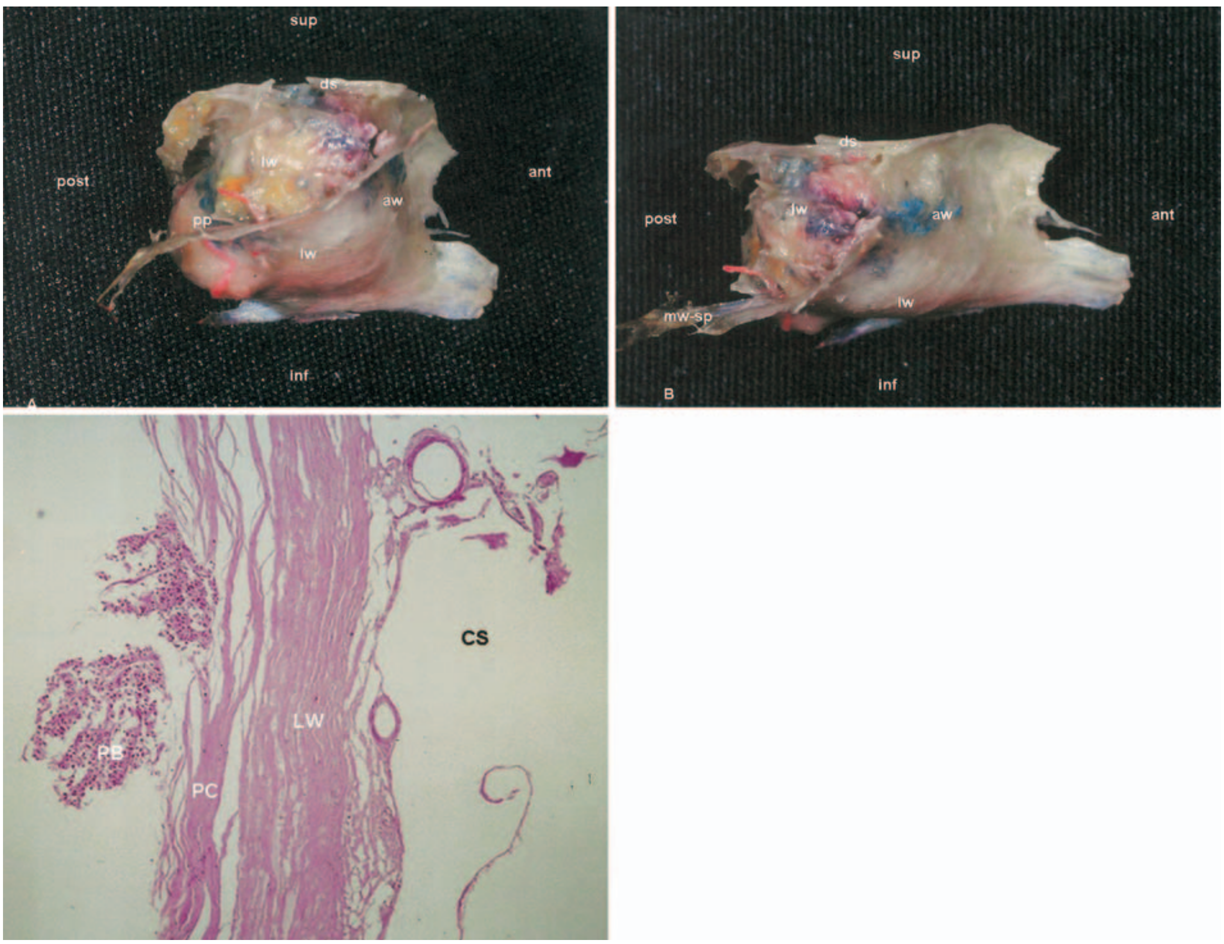


Fig. 2. (a and b) The dural sac that was left behind after the pituitary gland was microsurgically removed from the fossa: Note that the anterior wall (*aw*) and inferior wall (*iw*) of the sac (the walls that form the fossa) are smooth, and that the site where the inferior wall divides to form the lateral wall of the fossa is clear. The lateral wall (*lw*) is not as smooth as the anterior and inferior walls. Some adipose tissue is evident on the aspect of the lateral wall that faces the sinus cavity. The posterior portion (*pp*) of the pituitary gland is bulging posteriorly; (c) Histopathological examination of this specimen revealed a thick lateral wall (*lw*) composed of dura and fibroadipose tissue of the cavernous sinus (*cs*). Ant, anterior; ds, diaphragma sella; inf, inferior; mw-sp, sphenoidal part of the medial wall of cavernous sinus; pc, pituitary capsule; pg, pituitary gland; post, posterior; sup, superior. c, hematoxylin and eosin; original magnification, ×40

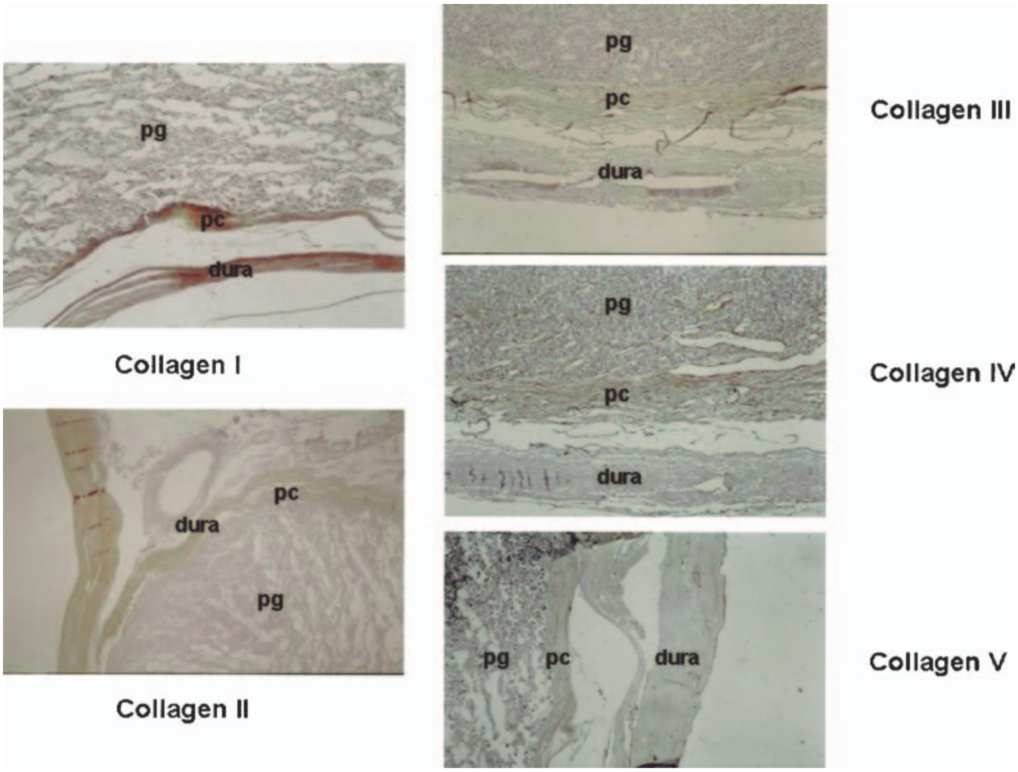


Fig. 3. Immunohistochemical examination revealed collagen types I and II in the pituitary capsule (*pc*) and in the lateral and inferior walls (d) of the fossa. However, collagen types III, IV and V were expressed in the pituitary capsule but not in the wall dura. pg, pituitary gland. Collagen I and II, original magnification, ×40, Collagen III, IV and V, original magnification, ×100

bulging from the posterior wall of the fossa. Histopathological examination of the above-mentioned sac external to the capsule revealed that it was, indeed, composed of thick dura (Fig. 2c).

*Collagen immunohistochemistry*

In all 12 specimens, the pituitary capsule was positive for collagen types I, II, III, IV and V, whereas the lateral and inferior walls of the sella were positive for only collagen types I and II (Fig. 3).

## Discussion

Cavernous sinus infiltration by pituitary adenomas is a clinically significant problem. The process by which these tumours invade the sinus is still a matter of debate. Nakasu *et al.* [21] assessed for cavernous sinus infiltration in 80 patients with pituitary adenomas. None of the micro-adenomas (15 patients) had infiltrated the sinus, and 21.5% of the macro-adenomas (14 of 65 tumours) exhibited infiltration. In another study of 106 pituitary adenomas, cavernous sinus infiltration was detected on magnetic resonance imaging in 44% of the cases [5]. Only 14% of the infiltrating tumours were micro-adenomas. Our clinical experience indicates that most pituitary adenomas that infiltrate the cavernous sinus are macro-adenomas. Also, tumour volume seems to be important with respect to parasellar infiltration.

In general, pituitary adenomas are considered biologically benign. However, some pathological reports claim that the incidence of dural infiltration by these neoplasms is close to 90% [28]. It is widely speculated that cavernous sinus invasion by pituitary adenomas is due to aggressive behaviour, and investigators have determined the growth rates of these tumours using Ki67 LI. However, reports document conflicting findings [18, 20, 30, 35]. Some studies that have evaluated Ki67 staining have shown a statistically significant difference between invasive and non-invasive adenomas [17, 18]. In contrast, an investigation of pituitary adenomas by Kawamoto and coworkers [12] revealed no relationship between proliferative index and cavernous sinus infiltration. In addition, Yokoyama *et al.* [35] studied 10 patients with pituitary adenoma and found no link between Ki67 expression and tumour invasiveness.

*Anatomy of the lateral wall of the pituitary fossa*

Traditionally, it has been accepted that the medial wall of the cavernous sinus is a thick dural layer located between the two clinoid processes superiorly and the sphenoid bone inferiorly [2, 19, 25, 29]. However, some detailed anatomical work has raised suspicions that this is incorrect. In an earlier study, Wislocki [33] reported that the pituitary capsule is derived from meningeal dura mater. Ciric [4] claimed that the pituitary capsule originates from primitive intracranial pia mater, and that the dura in the sella region develops from surrounding mesoderm. In 1980, Chi and colleagues [3] reported some findings from a study on human embryos and foetuses that disputed this pia dura origin of the capsule. They stated that the fibrous capsule that envelops the gland (the pituitary capsule) is almost identical to the capsule that surrounds salivary glands. Chi *et al.* concluded that the development of the pituitary capsule is related to the development of Rathke's pouch, not due to downward extension of pia arachnoid.

More recently, investigators have focused on the lateral wall of the pituitary fossa. However, reported findings and interpretations differ, and some authors claim that this wall does not actually exist. There is no consensus in the literature concerning the structure of the tissues that surround the pituitary gland. Some researchers have claimed that there is a wall composed of dura between the pituitary and the cavernous sinus [6, 14]. Kawase and coworkers [14] examined the meningeal architecture of the cavernous sinus in 10 adult cadaver heads. They identified the medial wall of the sinus (which they considered to be composed of meningeal dura) as loose and soft tissue that would allow easy invasion from or into the pituitary gland. Destrieux *et al.* [6] conducted a micro-anatomical study of human adult cadavers and one foetus. They described the pituitary gland lying within a dural sac formed by a fold of basal dura. The authors stated that this sac forms a snug enclosure around the hypophysis and isolates the hypophysis from all surrounding structures. Their conclusion was that the lateral portion of this dural sac forms the medial wall of the cavernous sinus. That study included no mention of how this sac relates to the dura on the floor of the pituitary fossa. According to Dolenc [8–10], pituitary adenomas invade the cavernous sinus via defects in the lateral wall of the fossa. This author points out that anatomical studies have demonstrated fenestrations in the lateral wall of the pituitary fossa. A recent report by Yasuda *et al.* stated that there is a distinct layer of dura between the pituitary gland and the cavernous sinus [34]. These researchers examined 40 specimens and identified this dural wall in each one. They did not report on the thickness or the histological structure of the wall, but stated that they observed no defects of the cavernous sinus medial wall in any of the samples. In line with these findings, we observed no fenestrations in the lateral walls of the pituitary fossae in multiple serial sections from 12 sellar-parasellar specimens.

Other reports have disputed the findings noted above. Kehrli and coworkers [15] investigated the sellar compartment in human foetuses and adults. They proposed that each lateral wall of the sella is composed of two structures, a dense glandular pituitary capsule and a loose fibrous bed that surrounds the gland. These authors suggested that there is actually no dural layer between the pituitary and the cavernous sinus. In another article, Dietemann *et al.* [7] evaluated the same data and came to the same conclusion. In accordance with this, an investigation of 10 cadaver specimens by Yokoyama and colleagues [35] revealed only a thin pituitary capsule and no dural layer between the cavernous sinus and the pituitary gland.

We feel that the confusion in the literature stems from the naming of the tissues lateral to the pituitary. Some reports indicate that the pituitary capsule forms the medial wall of the cavernous sinus [5, 6, 27]. However, comparison among articles reveals very little consistency in the names of the connective tissue layers lateral to the pituitary gland, and many reports suggest that certain walls/layers noted by other authors actually do not exist.

In our study, we removed the pituitary gland from its coverings in one of the head specimens. Macro- and microscopic examination of the area revealed that a distinct layer of dura surrounds the pituitary gland external to the capsule. Grossly, we also observed definite lateral walls on both sides of the fossa, and were able to visualize the yellowish adipose tissue that lines the cavernous sinus on the aspect of the lateral dura that faces the sinus cavity. We found that the dural layer that formed the inferior wall of the fossa was smooth, and that part of it appeared to be continuous with the sphenoidal portion of the medial wall of the cavernous sinus.

Our micro-anatomical findings clearly demonstrate that there are two separate structures lateral to the pituitary gland within the fossa: the pituitary capsule which immediately covers the gland, and the lateral wall of the sella, which is composed of dura. The pituitary capsule is a dense, tough, fibrous capsule which envelopes the gland. This covering was present in all 13 specimens we examined. This thin capsule completely encloses the pituitary and is similar to the capsules of other glands in the body. External to this are the lateral and inferior walls of the fossa, both exclusively composed of dura. In all specimens, we found that the dura of the inferior wall was much thicker than the lateral walls (mean 171 μm). This strong and thick layer lies between the pituitary and the sphenoid bone, and it divides in two at the inferolateral edge of the fossa. At this site, we observed the thicker layer divides to form a Y-shape with two thinner separate layers of dura. One of these was directed superiorly and formed the lateral wall of the sella. The other thinner layer continued laterally from the thick inferior fossa wall, and formed the sphenoidal part of the medial wall of the cavernous sinus superior to the sphenoid bone. The thin lateral walls of the fossa (mean thickness 85 μm) were approximately half as thick as the inferior wall. This lateral layer of dura continues superiorly and eventually joins the diaphragma sellae superolateral to the pituitary gland. However, we found that the thickness of the lateral walls varies greatly among individuals, and even the left and right thicknesses in the same person can differ. We observed the latter in two specimens. In both cases, the left wall was thicker than the right wall. In 17% of the head specimens in our study, the lateral walls of the pituitary fossa were extremely thin (average thicknesses for left and right sides 10 and 15 μm, respectively), and each appeared as a loose fibrous layer on histopathological examination.

We believe that variations in lateral wall thickness might explain the features of some pituitary adenomas. For example, it might explain why certain intrasellar adenomas show parasellar extension whereas other intrasellar adenomas of similar size do not. It could also be the reason why it is not uncommon to find a huge pituitary tumour with suprasellar extension that has also invaded the cavernous sinus on only one side. Further, thick lateral walls might explain why some massive adenomas show no cavernous sinus extension at all (Fig. 4). We contend that the presence and thickness of the lateral wall dura are key factors in cavernous sinus infiltration. Our theory is that, in a patient who has a thin lateral wall on one side of the fossa, a pituitary adenoma may easily invade the cavernous sinus unilaterally (Fig. 5A, B). In contrast, if a pituitary fossa has thick lateral walls, the tumour is unlikely to invade either cavernous sinus (Fig. 5C, D).

Some researchers have speculated and claimed that the pituitary capsule and the lateral wall of the sella are one and the same; however, we found these to be distinct tissues. In histopathological sections stained with Masson's trichrome, the pituitary capsule was a dark green–brown colour. In contrast, the dura was light green. This difference is what prompted us to evaluate

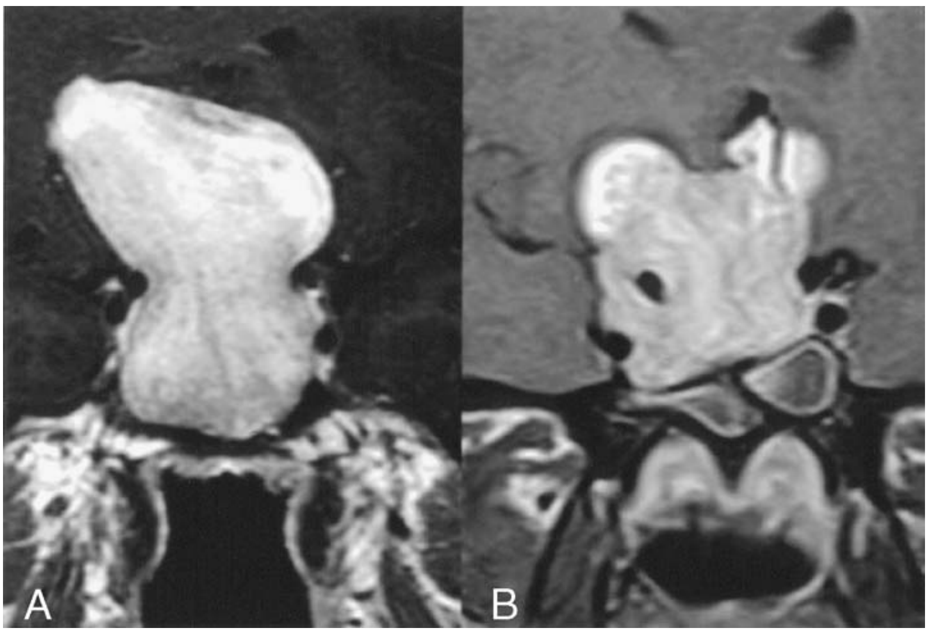


Fig. 4. (A) A contrast-enhanced, T1-weighted, coronal magnetic resonance image of a pituitary macro-adenoma demonstrates no invasion of the cavernous sinuses; (B) The same type of image shows a macro-adenoma from another patient with unilateral cavernous sinus invasion

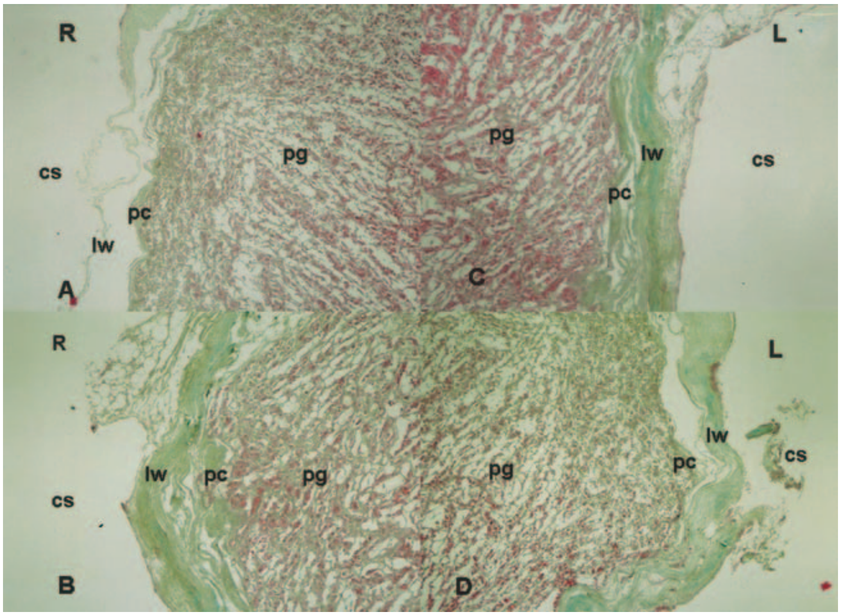


Fig. 5. A specimen in which the right (A) and left (B) lateral walls of the fossa were of different thicknesses (right wall dura 10 μm vs left wall dura 140 μm). In another specimen, both lateral walls are thick (C and D). Masson's trichrome, original magnification, ×40

the collagenous features of these structures. As detailed above, we did this using immunohistochemical methods.

*Collagen immunohistochemistry*

Collagen fibres form the largest component of connective tissue. Different body tissues contain different types of collagen. Collagen type I accounts for 90% of all collagen in the body. It is found in the connective tissue of skin, bone, tendon and organ capsules [26]. This type of collagen provides resistance to force, tension and stretch. Collagen type II is only found in cartilage and the vitreous humor. Type III collagen is frequently found in skin, muscles, and blood vessels. Collagen type IV is found in the basal laminae of epithelium and endothelium, and in the lens capsule [26]. This substance forms a supporting and filtrating barrier.

Our study is the first in the literature to have investigated the collagenous structure (collagen types I through V) of the pituitary capsule and the walls of the pituitary fossa. Dura mater is known to be mainly composed of collagen type I [13]. We observed similar distributions of collagen types I and II in the pituitary capsule and the dura mater of the lateral and inferior fossa walls. However, collagen types III, IV and V were detected only in the pituitary capsule, not in the walls. This proves that the pituitary capsule and the lateral wall of the sella are distinct structures.

Tumour-induced damage to the structures near a pituitary adenoma may be important in cavernous sinus invasion. Matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases which are able to degrade the extracellular matrix [32]. Previous studies have investigated pituitary tumours for MMP expression. MMP-9 is a type IV collagenase. Kawamoto and colleagues [13] were the first to document a relationship between MMP-9 expression in pituitary adenomas and cavernous sinus infiltration. The dura mater is mainly composed of collagen type I, but the authors also observed some immunopositivity for collagen type IV in the medial compartment of the dura mater. Later reports noted the same findings, since MMP-9 is related to aggressive behaviour and hormonal activity of pituitary tumours [23, 32]. Work by Turner *et al.* [32] also showed a link between angiogenic activity and MMP-9 expression in pituitary tumours; however, Yokoyama and colleagues [35] found no statistically significant relationship.

Our results indicate that the pituitary capsule is very rich in collagen type IV. Considering this, one would expect that a pituitary tumour that expresses MMP-9 would break down the capsule. If the capsule is damaged and the lateral wall of the fossa is thin or weak, the tumour might infiltrate the cavernous sinus [13, 23, 32]. We believe that, in addition to MMP-9 expression by pituitary adenomas, other factors contribute to tumoural invasion of the cavernous sinus. We strongly suspect that the structure of the lateral wall of the sella is an important element. A relatively thick and continuous dural wall lateral to the tumour forms a stronger barrier against cavernous sinus infiltration.

## Conclusion

1. The pituitary gland is enveloped by a dense fibrous capsule. External to this there is a distinct lateral wall of the pituitary fossa. This wall is composed of dura, and it forms a barrier between the pituitary and the cavernous sinus.
2. The pituitary capsule and the lateral wall of the sella have different collagen profiles.
3. We conclude that cavernous sinus infiltration by pituitary adenomas results from a combination of two main elements: weakness of the anatomical barrier (the lateral wall of the fossa) and biochemical destruction of collagen fibres in the pituitary capsule.

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## Comments

This is a very interesting and excellent series of cadaveric studies of pituitary dura, and compares this with the 'invasiveness' or otherwise of a small series of pituitary adenomas.

The paper sets out to answer whether there is a true pituitary capsule (there is, it has a particular collagen type typical of 'glands') and whether this can answer why apparently benign adenomas can invade the cavernous sinus – the true dura different collagen type) is very thin and can be very unilaterally so on only one side, over the CS.

A wonderful paper which deserves a place in my list of references.

*M. Powell*
London

The authors describe a study, in a small number of patient, of the lateral wall of the cavernous sinus and the concept of cavernous sinus invasion. Their illustrations show in a fairly convincing way that there may be a separate collagenous thin capsule to the pituitary gland proper. This has been disputed in the past and it would be essential for the discussion to recognize that there have been differences of opinion with regard to this and to put their findings into perspective with regard to the controversy that exists around the pituitary capsule, that is whether it consists of compressed normal pituitary gland or whether it is a separate mesenchymal structure.

*E. R. Laws*
Charlottesville

Correspondence: Selçuk Peker, PK 240, 34711 Kadikoy, Istanbul, Turkey. e-mail: peker@atlas.net.tr