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# Progesterone Receptors in Arachnoid Cysts

## An Immunocytochemical Study in 2 Cases

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## Summary

We report 2 cases of arachnoid cysts, one with a retrocerebellar and the other with a left temporal localization, in which immunohistochemical studies had been conducted. The results of the immunohistochemistry on the presence of carcino-embryonic antigen (CEA) and glial fibrillary acidic protein (GFAP), and of the scanning- and transmission electron microscopy revealed the cyst lining to be identical to subdural neurothelium. Progesterone receptors were found in the nuclei of cells lining the cyst, which also suggests the similarity of the cyst lining to arachnoid granulations and meningiomas as derivatives of subdural neurothelium, which also possess progesterone receptors.

*Keywords:* Arachnoid (cyst, granulation); meningioma; progesterone receptors.

## Introduction

Intracranial arachnoid cysts are unnatural intracranial cavities filled with a CSF-like fluid, and enclosed by transparent membranes resembling arachnoid mater, which border the dura mater at the roof of the cyst, and on other sides border the true arachnoid mater of surrounding subarachnoid spaces and cisterns. Because most arachnoid cysts are asymptomatic, they used to be an incidental finding, but with the advent of the current imaging techniques, today arachnoid cysts are observed much more often, showing an incidence of 0.3% on CT-scans [20]. There is a predominance of males, and a preference for the left side and the temporal fossa. Less common localizations are the posterior fossa, the sellar and the pineal areas.

Since arachnoid cysts are closed cystic cavities usually lacking communication with surrounding CSF spaces, it is plausible that the cyst lining maintains cyst fluid volume by secretion of fluid. Previous ultrastructural studies have demonstrated that the lining of arachnoid cysts consists of the layer of arachnoid mater that borders the dura mater [6, 28], and which has been designated as the subdural neurothelium or subdural mesothelium [1, 18, 23]. Moreover, subdural neurothelium is a component of arachnoid granulations [2, 22], and $Na^+K^+$-ATPase activity has been demonstrated by enzyme cytochemistry in the lining of arachnoid cysts as well as in that of arachnoid granulations, indicating a capacity for fluid secretion [7, 8]. Subdural neurothelium may also be the tissue from which meningiomas are probably derived. These tumours have been shown to possess receptors for progesterone rather than for oestrogens [3, 10, 25]. We have recently demonstrated by a ligand-binding assay the presence of progesterone receptors in the lining of arachnoid cysts and in arachnoid granulations [30], but the precise localization of the receptors has not been established.

## Patients and Methods

*Case Reports*

*Case 1:* A 32-year-old male with complaints of headaches, dizziness and a feeling of malaise, showed no abnormalities upon neurological examination, but the CT-scans showed a large space with the density of CSF behind the cerebellum, resembling a retrocerebellar arachnoid cyst. The MRI-scan essentially showed the same findings and the presence of a membrane at the inferior limit of the cyst separating it from the cisterna magna (Fig. 1 a). Upon operation the dura of the posterior fossa was exposed through a posterior fossa craniectomy. The dura was opened without cutting the cyst membrane. Upon puncturing the cyst a clear and colourless CSF-like fluid was obtained from it. After opening the cyst biopsies were taken from the roof of the cyst immediately underlying the

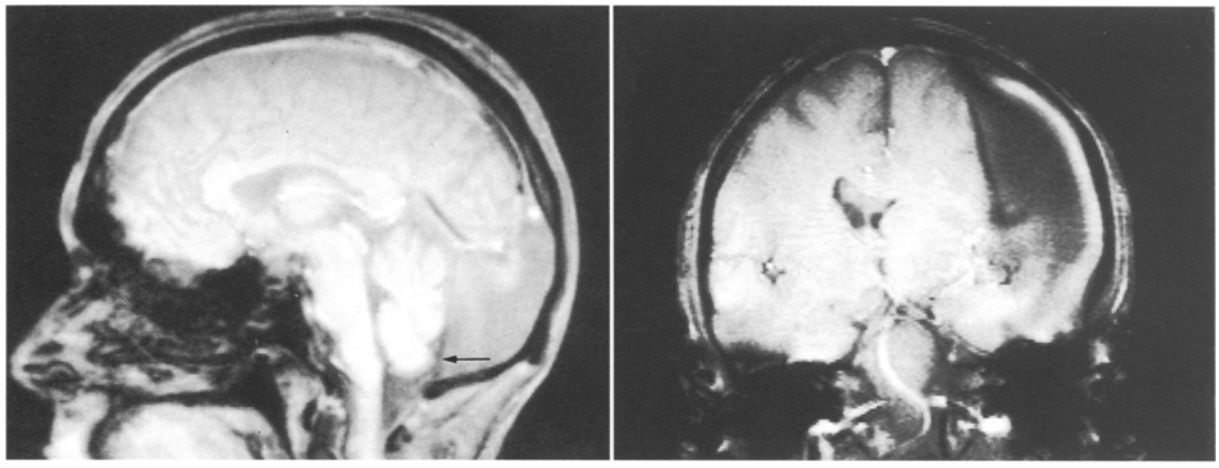


Fig. 1. (a) $T_2$-weighted gradient echo image of case 1, showing a membrane (arrow) as a dark line, being the bottom of the arachnoid cyst and separating the cyst lumen from the cisterna magna. (b) $T_2$-weighted gradient echo image of case 2 showing large left temporal arachnoid cyst

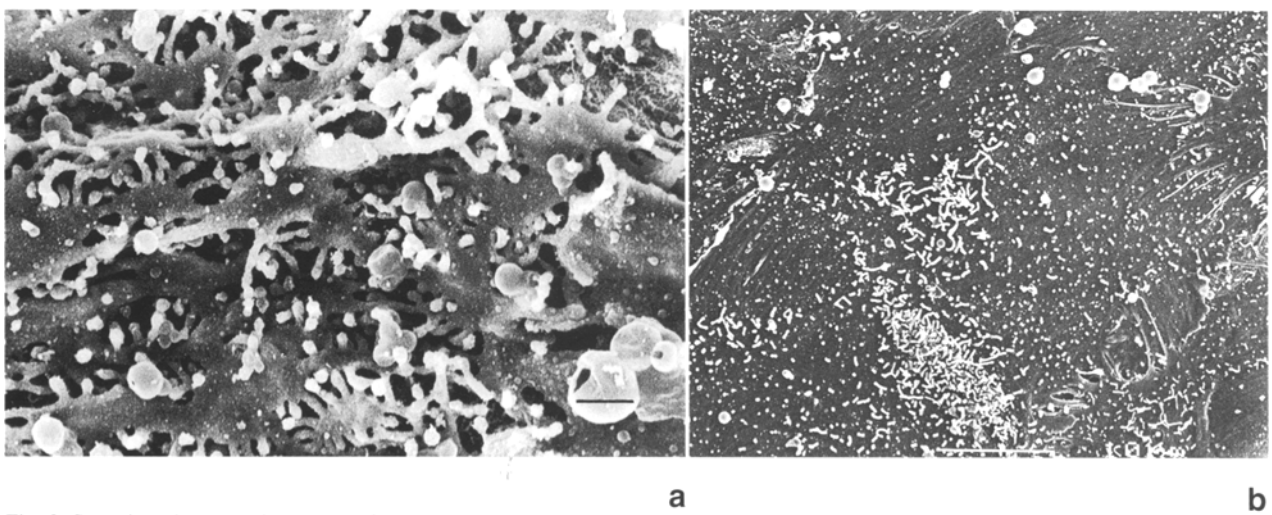


Fig. 2. Scanning electron microscopy of cyst wall. (a) In case 1 the luminal surface showed stubby microvilli and fenestrations. Scale bar: 1 µm. (b) In case 2 there were a few fenestrations; most microvilli were stubby, while some were balloon-like, and others were elongated into thread-like projections. Scale bar: 10 µm

dura; some were immersed in 2% buffered glutaraldehyde solution after fixation on a piece of styrofoam with thin pins to prevent its shrinking and loss of orientation; others were immersed in buffered formalin. After the cyst was emptied, a thin transparent membrane was seen at the inferior limit of the cyst, which separated the cyst from the underlying cisterna magna. Ample fenestration of the cyst was performed. The biopsies in buffered formalin were routinely embedded in paraffin and processed for immunohistochemical detection of carcino-embryonic antigen (CEA) and glial fibrillary acidic protein (GFAP). Immunohistochemistry for oestrogen and progesterone receptors using the biotin-streptavidin immunoperoxidase technique was performed on 4 µm paraffin sections; as antigen retrieval method the sections were heated in citrate buffer of pH 6.0 at 100° C for 10 min; the monoclonal anti-oestrogen and anti-progesterone receptor antibodies were purchased from Immunotech (clone ER1 D5) and Eurodiagnostics (clone 1A6), respectively. The biopsies fixed in glutaraldehyde solution were processed for scanning and transmission electron microscopy.

*Case 2:* A 63-year-old male complained of headaches since he fell from a couch 6 months ago. He also exhibited occasional loss of speech. CT-scans showed a large hypodense lesion in the left temporal area, extending from the base of the skull to the vertex, and exerting compression on adjacent structures. On the MRI-scan

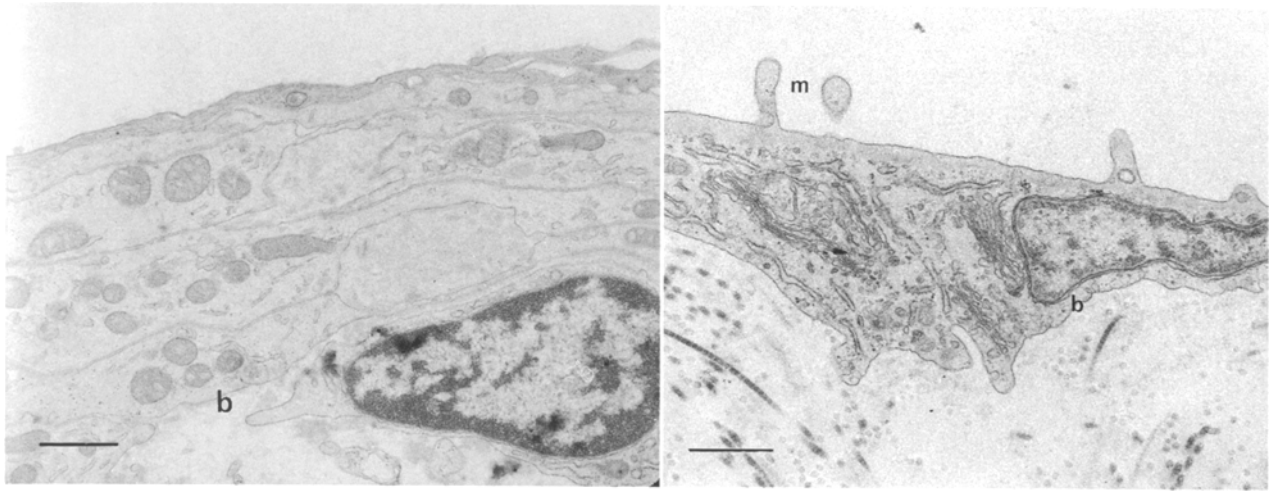


Fig. 3. Transmission electron microscopy of cyst wall. (a) In case 1 there were multiple layers of clear as well as electron dense cells, resting on an incomplete basal lamina (*b*). The cells contain mitochondria and various vesicles. (b) In case 2 there was a single layer of lining cells showing several microvilli (*m*) on the luminal side, and containing a nucleus with marginated chromatin, as well as various organelles. There was an incomplete basal lamina (*b*) underlying the cells, separating them from the dura with its collagen fibres. Scale bar: 1 μm

the lesion had the signal intensity of CSF (Fig. 1 b). Exploration through a left temporoparietal craniotomy and opening of the dura revealed the cyst which occupied a large part of the frontal and parietal areas and most of the temporal fossa. The roof of the cyst was a thin transparent membrane immediately bordering the dura. At the floor of the cyst a thick opaque membrane covered the arachnoid of the insula, as well as that of the indented parietal and frontal lobes, since the frontal and parietal opercula had not developed. Biopsies were taken for immunohistochemistry and electron microscopy. Ample fenestrations were made to ensure communication of the cyst with the subarachnoid CSF. Some of the biopsies were fixed in formalin, and embedded in paraffin. Sections were processed for immunohistochemistry for GFAP, CEA, as well as progesterone and oestrogen receptors, as described above. Other biopsies were fixed in glutaraldehyde, and processed for scanning and transmission electron microscopy.

## Results

*Immunohistochemistry* of the cyst lining of meningothelial cells showed neither GFAP nor CEA immunoreactivity in case 1. In case 2 there was no immunostaining for GFAP, and a very faint staining for CEA.

*Scanning electron microscopy* of the biopsies from the cyst walls showed that the surface of the cyst wall exhibited typical fenestrations and stubby microvilli of 0.14–0.7 μm in case 1, fenestrations and microvilli of diverse shape in case 2 (Fig. 2 a and b).

*Transmission electron microscopy* of the biopsies from the roof of the cyst showed the cyst lining to consist of multiple layers of flattened, clear as well as more electron dense cells resting on an incomplete basal lamina, exhibiting microvilli, interdigitating processes, and containing nuclei with marginated chromatin, as well as other organelles including mitochondria and various vesicles (Fig. 3 a and b).

*Light microscopy* of the sections for steroid receptor assay showed loose connective tissue with variable cellularity in which more or less collapsed cysts and cleft-like structures were seen lined by flattened meningothelial/fibroblast like cells. Focal aggregation of less flattened lining cells was present inducing bulging out into cysts and clefts.

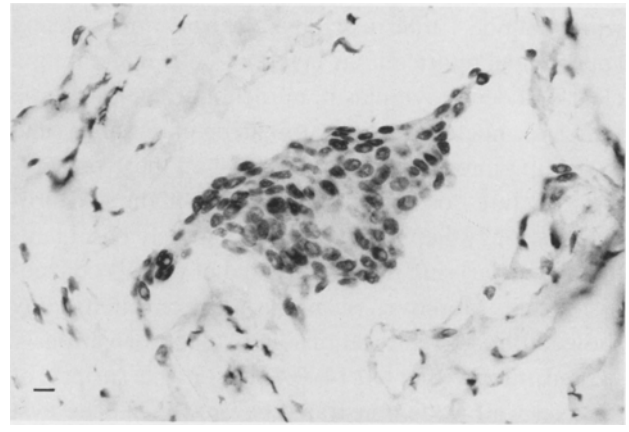

Fig. 4. Oestrogen receptor-immunohistochemistry of the same tissue in case 1, showing lack of expression of the receptor. Scale bar: 10 μm

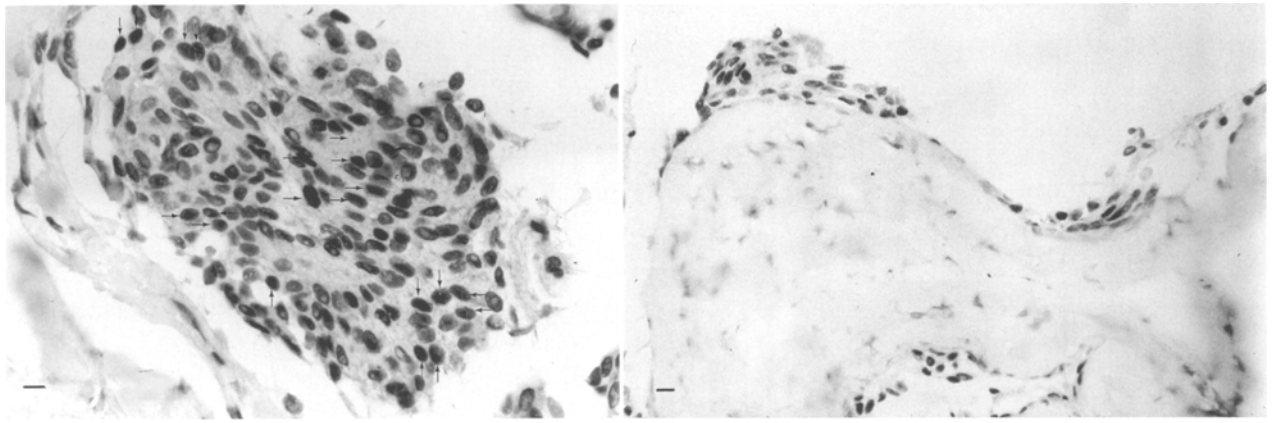


Fig. 5. Progesterone receptor-immunohistochemistry of 4 µm paraffin section of arachnoid cyst wall. (a) In case 1 there was weak to moderate expression of the receptor in the nuclei of the meningothelial cells (arrows). (b) In case 2 a folded cyst wall showed expression of the progesterone receptor in the most superficial layers. Scale bar: 10 µm

*Immunohistochemistry* for oestrogen and progesterone receptors showed the oestrogen receptor determination to be negative (Fig. 4). Progesterone receptor expression, however, was present in the nuclei of the lining cells along the clefts and cysts, especially in the bulging cellular foci (Fig. 5 a and b). This nuclear progesterone receptor expression was weak to moderate and seen in 25–50% of the nuclei of the lining cells. Other cells were negative. Sections incubated with phosphate-buffered saline instead of specific monoclonal antibodies served as negative controls.

## Discussion

Regarding the nature of the cyst wall, light microscopy showed it to consist of cleft-like structures lined by flattened meningothelial or fibroblast-like cells, which upon transmission electron microscopy appeared as multicellular layers of cells containing a clear or a dense cytoplasm, mitochondria, pinocytotic vesicles, nuclei with marginated chromatin, and exhibiting interdigitating processes; all these presenting a picture consistent with that of subdural neurothelium [6, 7]. Separated by an incomplete basal lamina, the underlying tissue consisted of (dural) connective tissue. Moreover, scanning electron microscopy showed typical fenestrations and stubby or variously shaped microvilli of 0.14–0.7 µm on the surface of the cyst wall as demonstrated before [6, 7]. The cyst was precluded to be a neuro-epithelial cyst, since glia or ependyma as constituents of the cyst lining was inconsistent with the lack of immunostaining for GFAP, while choroid plexus epithelium as a lining could also be excluded by the negative staining for CEA [14, 16].

The presence of progesterone receptors in meningiomas is a phenomenon that has been extensively studied [3, 10, 25], and which has been applied to control the growth of the tumours by means of the anti-progestin mifepristone (RU 486) [12, 17]. Meningiomas have conventionally been considered to arise from arachnoidal cap cells, a designation of the arachnoid cell layer bordering the dura [15], coincident with the subdural neurothelium (or mesothelium) in ultrastructural studies. Estimating the presence of progesterone receptors in other tissues containing subdural neurothelium, indeed an arachnoid granulation and the lining of arachnoid cysts proved to possess progesterone receptors [30]. In the present study the progesterone receptors could be localized in the nuclei of the subdural mesothelial cells lining the arachnoid cyst. Like other steroid receptors, the progesterone receptor is localized in the cytoplasm, where it can readily be reached by the lipophilic steroid ligands. After binding the steroid ligand, the receptor-ligand complex has been shown to move into the nucleus, in which it is assumed to interact with the nuclear DNA [13]. The receptor molecule possesses a so-called DNA response element, a domain containing two so-called zinc-fingers which can interact with the hormone regulatory element of the DNA molecule, where the interaction elicits transcription of the hormone dependent gene [4, 27].

The occurrence of progesterone receptors in arach-

noid granulations suggests an influence of progestins on the function of arachnoid granulations, namely CSF absorption. Another steroid, dexamethasone, has been shown to enhance CSF absorption in feline arachnoid villi [19]. It is conceivable that progestins also exert an influence on CSF absorption in arachnoid granulations, which is presumably inhibitory. It may explain the finding of increased CSF volumes in women in the premenstrual period, which has tentatively been held responsible for the premenstrual syndrome [11]. Assuming the occurrence of progesterone receptors in arachnoid granulations as primary, bearing upon their function in CSF absorption, the subdural neurothelium as the factor in common may account for the presence of progesterone receptors in meningiomas.

Although arachnoid cysts that do not block CSF pathways, do not cause intracranial pressure elevation, their presence is not entirely harmless. This is because arachnoid cysts generally do not communicate with surrounding CSF spaces and therefore their fluid content does not constitute a displaceable fluid volume that easily shifts into other CSF spaces during movements of the head, and this makes the cysts to behave as an incompressible mass, (reducing craniospinal compliance in terms of the intracranial pressure/volume relationship). They may conceivably exert pressure on surrounding brain especially during decelerations or accelerations of the head, with consequent compressive ischaemia in surrounding areas as demonstrated by blood flow imaging [26], to the effect that in the young brain growth retardation of surrounding brain structures may result. Extreme cases in which the development of the temporal lobe is arrested in association with the presence of a temporal arachnoid cyst, are known as the syndrome of "temporal lobe agenesis" [24]. In pathophysiological respects and pertaining to the indication for treatment, arachnoid cysts should be differentiated from other cysts containing a CSF-like fluid, like traumatic leptomeningeal cysts, porencephalic cysts, and cavities remaining from infarctions and from the removal of large tumours; all these cysts actually arise from a shortage of brain tissue and therefore we have classified them as ex vacuo type of cysts [9]. Because these cysts are the result of a shortage of brain tissue and generally exhibit communication with surrounding CSF spaces, they do not reduce craniospinal compliance or cause intracranial pressure elevation, and therefore do not require surgical treatment. The treatment of arachnoid cysts aims at draining the cyst fluid contents, by shunting to the peritoneal cavity, or by opening the enclosing membranes and establishing communication with surrounding CSF spaces.

With respect to retrocerebellar arachnoid cysts in particular, a differentiation from other CSF accumulations in the area, such as a Dandy-Walker syndrome, a persistent Blake pouch, or a megacisterna magna, is necessary [29]. In the present case these lesions have been excluded by the demonstration of a membrane separating the cyst from the cisterna magna. The present case also lacks a spinal extension, which has typically been reported for retrocerebellar arachnoid cysts [5]. Temporal arachnoid cysts, on the other hand, are known to have a propensity for bleeding, and an intracystic haemorrhage progressing into a subdural haematoma may be a cause for symptoms of intracranial pressure elevation [21].

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## Comments

The authors report 2 cases of arachnoid cysts in which immunohistochemical studies and scanning and transmission electron-microscopy revealed the cyst lining to be identical to subdural neurothelium. An important finding is that the walls of the cyst show progesterone receptors and that they are localized in the nuclei of the subdural mesothelial cells.

The study confirms the similarity of arachnoid cysts to normal lepto-meningeal cells. Previous studies have already demonstrated the presence of progestin receptors in human normal lepto-meninges in adult (1). The possible influence of these receptors to a phenomenon of secretion-absorption within the cysts may explain changes in their volume.

The paper, even if the number of cases is limited, does, however, provide interesting information concerning anatomy and physiology of the wall of arachnoid cysts.

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