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Cystic lesions of the sellar-suprasellar region — diagnosis and treatment

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Abstract

The differentiation of cystic lesions located in the sellar-suprasellar region is a significant problem in clinical practice because of the similarities in their clinical, radiological, and even histopathological picture. Arriving at the right diagnosis is vital for taking appropriate therapeutic decisions.

The most frequent clinical manifestation of lesions located in the sellar-suprasellar region is headache. It often co-exists with symptoms of anterior pituitary gland insufficiency or hyperprolactinaemia caused by compression of the pituitary stalk. Diabetes insipidus, obesity, mental disorders, and circadian rhythm disorders may be associated with lesions penetrating the suprasellar space. It is extremely important to rule out the possible coexistence of pituitary microadenoma and Rathke's cleft cyst, which became possible with the use of ^{11}C-methionine positron emission tomography/computed tomography (C-MET PET/CT). Reports from literature indicate that pituitary microadenoma may coexist with Rathke's cleft cyst in 10% of patients. Cystic lesions of the sellar-suprasellar region should also be differentiated from a cystic pituitary adenoma or abscess.

The first-choice therapy in symptomatic cystic lesions of the sellar-suprasellar region is neurosurgery, which usually relieves headache and improves vision impairment, while less frequently restores normal pituitary function. In suprasellar lesions, neurosurgery may trigger or aggravate pre-existing symptoms of damage to the hypothalamus. Patients undergoing neurosurgery for cystic lesions located in the sellar-suprasellar region should be monitored for a few years due to their high recurrence rate, potential malignant transformation of these lesions, and possible adenoma development through metaplasia. The advent of targeted therapy of the BRAF/MEK pathway is associated with new therapeutic opportunities for patients with craniopharyngiomas. **(Endokrynol Pol 2018; 69 (2): 212–220)**

Key words: *cystic lesion, sellar-suprasellar region, diagnosis, treatment*

Introduction

The diagnosis and treatment of cystic lesions located in the sellar-suprasellar region requires an interdisciplinary approach with the participation of a radiologist, ophthalmologist, endocrinologist, and a neurosurgeon. These lesions have been detected increasingly more often since various imaging techniques became more accessible, which also means that it is necessary to differentiate incidentalomas from lesions with serious clinical consequences. Determination of the cause of the observed lesion is crucial for choosing the right treatment option. Management of Rathke's cleft cysts (RCC) with benign course differs from that of RCC-mimicking craniopharyngiomas, which are locally aggressive [1]. Apart from the aforementioned Rathke's cleft cysts and craniopharyngiomas, cystic lesions of the sellar-suprasellar region include arachnoid cysts, secondary empty sella syndrome, and cystic adenomas, as well as less frequent xanthogranulomas, and epidermoid cysts [2]. Cystic lesions of the sellar-suprasellar region have not been described in Polish literature so far. In foreign literature the reports are also few, and they lack a comprehensive approach.

The aim of this paper is to highlight the problem of cystic lesions located in the sellar-suprasellar region in the context of their epidemiology, etiopathogenesis, diagnosis, and therapy.

Rathke's cleft cyst

Epidemiology

Rathke's cleft cyst is the most frequent incidentaloma of the sellar-suprasellar region. Its incidence based on autopsy is approximately 20% [3]. Symptomatic Rathke's cleft cysts are, however, uncommon. Their peak incidence falls between the fourth and the sixth decade of life. They are three times more frequent among women than among men [1].

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Etiopathogenesis

Rathke's pouch arises from the craniopharyngeal duct. In embryogenesis, cells of the anterior and the posterior wall of the pouch give rise to the anterior pituitary and pars intermedia, respectively. These structures come into contact with the infundibulum, which is made of nervous tissue. When the lumen of the pouch forms a cleft that fails to regress, it leaves a space filled with fluid between the pars nervosa and the ectoderm. Hence, Rathke's cleft cyst is found in pars intermedia between the anterior and posterior lobes of the pituitary gland. In some cases, Rathke's cleft cyst also spreads to the suprasellar space.

In approximately 50% of cases, inflammation around the cyst is observed, which can be visualised on magnetic resonance imaging (MRI) [4]. Autopsies also showed the presence of cyst wall metaplasia in 9–39% of patients [2].

Clinical picture

Clinical symptoms associated with Rathke's cleft cyst are caused by elevated pressure in the perisellar region. The most common clinical manifestation is headache. The pain is usually nonpulsating, episodic, and located in in the frontal or in the retro-orbital region [5]. Headaches may however have a non-specific location and nature. If the cyst is large, it may compress the optic chiasm resulting in vision impairment [6, 7].

Although Rathke's cleft cyst is mostly diagnosed incidentally, endocrine dysfunction is found in 80% of patients with symptomatic lesions [3]. Laboratory deviations usually include hyperprolactinaemia and insufficiency of the gonadal, the adrenal, and less frequently of the thyroid axis [8]. These disorders are rather associated with features of inflammation visualised on MRI than with the size of the cyst. In rare cases of lesions penetrating the suprasellar space, diabetes insipidus is also observed. The most common complaints related to endocrine dysfunction include secondary amenorrhoea, reduced libido, and impotence [1].

Diagnostic imaging

Rathke's cyst is visualised on magnetic resonance imaging as a lesion located in the intermediate lobe of the pituitary. Its largest diameter usually does not exceed 20 mm [9, 10]. The cyst may have varying intensity against the cerebrospinal fluid, although it is more often hypointense in T1-weighted images and hyperintense in T2-weighted images. RCC image captured on MRI is described as "an egg in a shell" [11]. The enhancement of the cyst wall following contrast administration suggests inflammation or metaplasia.

Treatment

It is assumed that symptomatic lesions require excision, although disease dynamics should be taken into account when making the decision. The removal of Rathke's cleft cyst is associated with a high risk of diabetes insipidus as a consequence of frequently observed adherence of the cyst walls to the infundibulum. If signs of hypopituitarism are present prior to surgery, they usually persist after neurosurgical treatment.

Patients should be monitored for at least five years following surgery because the risk of recurrence may even reach 50%. This risk is particularly high when inflammation around the cyst is observed. It has been demonstrated that antibiotic therapy may reduce the risk of recurrence in such cases [12]. Radiotherapy may prove effective in the treatment of recurrent Rathke's cleft cysts, although available evidence is insufficient.

Asymptomatic Rathke's cleft cysts require observation, although its duration has not been established so far. It is important to remember that a growing number of studies indicate a possible transformation of metaplastic Rathke's cleft cyst into craniopharyngioma [4, 13, 14]. Based on the work of Raluca Trifanescu et al. [1], we have proposed an up-to-date diagnostic and therapeutic algorithm for patients with Rathke's cleft cyst (Fig. 1).

Coexistence of Rathke's cleft cyst with pituitary adenoma

Recent studies have shown the presence of stem cells in the pituitary and their role in tumourogenesis of the sellar-suprasellar region [15]. Cells related to neoplasmatic changes, co-expressing cytokeratins, GFAP and S-100, have been found in Rathke's cleft cyst. The occurrence of cells with a similar phenotype in pituitary adenomas seems to be associated with invasiveness and recurrence of tumours [16].

Several attempts have been made so far to determine the coexistence of pituitary adenomas with Rathke's cleft cysts [17]. It is a challenge because an adenoma located in a pituitary gland compressed by the cyst often remains undetectable on MRI. Retrospective studies found no statistically significant concurrence of these pathologies [18]. However, Hidetoshi Ikeda and Genichiro Ohhashi, who prospectively analysed 308 patients, demonstrated concomitant occurrence of an adenoma in 34% of inflammatory Rathke's cleft cysts [19]. Most adenomas (74%) were visualised in ^{11}C-methionine positron emission tomography/computed tomography [C-MET PET/CT], while other adenomas were diagnosed in histopathological examination. It is worth noticing that the most common coexistent adenomas included GH-omas and ACTH-omas. It supports

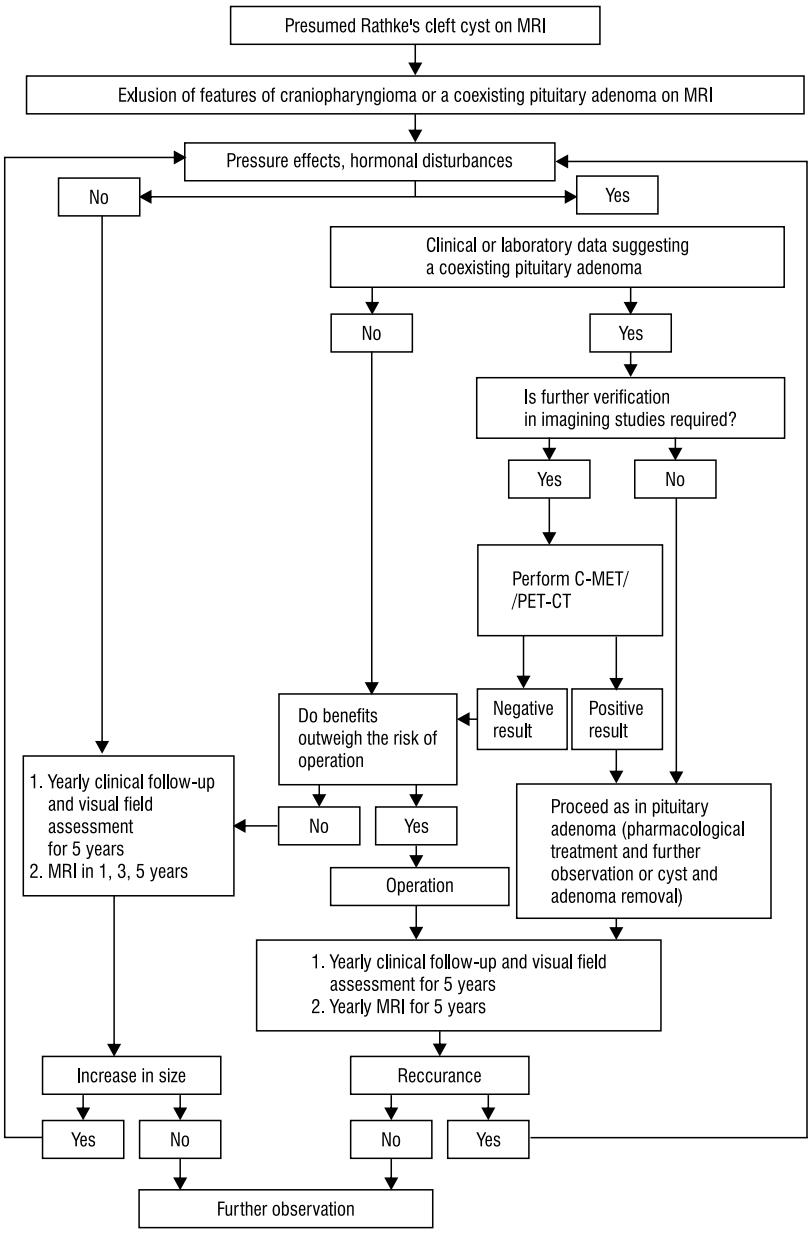

Figure 1. *Managment algorithm for Rathke's cleft cyst*

the hypothesis that these lesions might be associated with metaplasia of cells in the anterior pituitary, as a result of inflammation around the cyst. Further studies also confirmed high sensitivity of C-MET PET/CT in the detection of pituitary microadenomas invisible on MRI [20].

Also, ^{18}F-deoxy-glucose positron emission tomography combined with computed tomography (^{18}F-FDG PET/CT) sometimes reveals benign lesions of the sellar-suprasellar region [21]. However, the low sensitivity of this method for detecting pituitary adenomas limits its utility in diagnosing lesions undetectable on MRI [20].

Craniopharyngioma

Epidemiology

The incidence of craniopharyngioma is approx. 1–2/1,000,000/year. Peak incidence is observed twice during the lifetime: in the 1st and the 2nd decade and between 50 and 70 years of age [22]. Similarities between Rathke's cleft cyst and craniopharyngioma may be so strong that differentiating one from the other is only possible in postoperative immunohistochemical examination. Moreover, there are lesions with coexistent features characteristic for both of these pathologies, which may be due to the fact that they share a common origin.

Etiopathogenesis

Craniopharyngiomas occur in two histopathological variants: adamantinomatous and papillary. The adamantinomatous variant occurs both in children and adults, while the papillary variant is characteristic of the adult population. Recent studies have shown that histopathological differences are caused by different genetic mutations.

In adamantinomatous craniopharyngiomas, *CTNNB1* mutation was detected. It is responsible for β-catenin translocation from cell membrane to the nucleus. The incidence of this mutation among adamantinomatous craniopharyngiomas is estimated at 81–100% based on genetic tests and immunohistochemical staining [23, 24].

BRAF V600E mutation is characteristic of the papillary variant of craniopharyngioma. Its occurrence can be confirmed with immunohistochemical staining using VE1 monoclonal antibody, detecting BRAF V600E protein epitope [24]. The incidence of this mutation in papillary craniopharyngioma is estimated at 95–100%. The existence of craniopharyngioma types combining the features of adamantinomatous and papillary variants is still being discussed [25].

Despite a few theories on the development of craniopharyngiomas, none of them has been proven to date. In their recently published study, Liu Y. et al. demonstrated the existence of triggering receptors exposed on myeloid cells-1 (TREM-1) in papillary craniopharyngiomas and in Rathke's cleft cysts with squamous metaplasia, but not in adamantinomatous craniopharyngiomas [26]. This finding supports the hypothesis of sequential transformation of the sellar-suprasellar cyst lesions [2]. In this approach, Rathke's cleft cyst is on one end of a pathologic continuum and papillary craniopharyngioma on the other, while mixed-type lesions such as xanthogranulomas fall between these two pathologies. The adamantinomatous variant is likely to originate from the remnants of the craniopharyngeal duct, similarly to Rathke's cleft cysts. This would account for its common occurrence in children.

A recently published study demonstrated that immunohistochemical staining using VE1 allowed the diagnosis of Rathke's cleft cyst to be changed to that of papillary craniopharyngioma in three out of 33 cases. Thus, immunohistochemical staining using VE1 appears to have great clinical significance and should be performed particularly in sellar-suprasellar cyst lesions with squamous metaplasia [27].

Clinical picture

Clinical symptoms usually resemble those observed in symptomatic Rathke's cleft cyst. However, since craniopharyngiomas at their early stage of development usually remain clinically silent, they are diagnosed when their size is large, causing symptoms associated with the compression of structures forming the floor of the third ventricle and elevation of intracranial pressure [28]. Thus, symptoms related to craniopharyngioma result from the mass effect and raised pressure in the intrasellar space. Just as in Rathke's cleft cysts, vision impairment (62–84%), headache, and endocrine dysfunction (52–87%) occur and the symptom characteristics are not different from those observed in Rathke's cleft cyst. However, symptoms caused by compression of hypothalamic structures, including secondary amenorrhoea, obesity, circadian rhythm disturbances, and cardiovascular disorders, are much more frequent than in patients with Rathke's cleft cyst [29–31]. They are difficult to treat, and their incidence and severity may increase during therapy from approx. 30% to as many as 80% of cases [32]. This affects the quality of patients' lives [30]. Patients with craniopharyngioma also present with neuropsychiatric changes [33], including short-term memory loss related to the compression of mammillary bodies. Complaints of impaired memory may be reported by as many as 50% of patients and they are more common among older subjects. Patients with delayed diagnosis may present with hydrocephalus [34–36]. Craniopharyngiomas are often responsible for central diabetes insipidus as a result of damage to subthalamic nuclei or the upper part of the pituitary stalk, just above the sellar diaphragm. Lesions restricted to the intrasellar space do not cause neurogenic diabetes insipidus [37]. In some cases, diabetes insipidus may have an insidious course with symptoms masked by secondary hypothyroidism and adrenal failure. In such cases, fluid retention resulting from anterior pituitary failure compensates for water loss caused by vasopressin deficiency [38–40]. Polyuria and polydipsia develop once hormone substitution is started.

Additionally, diabetes insipidus without excessive thirst, so-called adipsic central diabetes insipidus, constitutes a serious risk for patients. Its rare occurrence is found in cases in which proliferative process damages osmoreceptors in the anterior part of the hypothalamus [41]. This suppresses the feeling of thirst, increases plasma osmolality, and produces hypernatraemia. The condition ultimately leads to reduced brain volume and intracranial or subarachnoid haemorrhage [42]. However, central diabetes insipidus in patients with craniopharyngioma most commonly develops as a postoperative complication, being the consequence of pituitary stalk transection. Triphasic response to this damage is an additional challenge in the diagnosis and therapy [43]. Initially, during the first few days after surgery, clinical symptoms

typical of diabetes insipidus are observed. These are followed by water reabsorption in distal nephrons as a result of ADH secretion from neurons and transient regression of symptoms. In the third phase, typical DI symptoms recur. Surgery-induced DI with normal thirst is reported in 81–96% of patients and adipsic diabetes insipidus in 7.1% of cases [44]. One study demonstrated that tumour size exceeding 3.5 cm and hydrocephalus were risk factors for adipsic diabetes insipidus after craniopharyngioma excision. On the other hand, radiotherapy did not increase the risk of adipsic diabetes insipidus [45].

Diagnostic imaging

Craniopharyngioma is usually suspected on the basis of MRI findings. It usually appears as a lesion located in the sellar-suprasellar region with the largest diameter exceeding 20 mm [46]. The lesion is hypointense in T1-weighted images and hyperintense in T2-weighted projections. Cystic components of the tumour are usually hyperintense in T1- and T2-weighted images [47]. Characteristic features include calcifications within the lesion [48], which are apparent on CT scans and enhancement of tumour wall after contrast administration on MRI. Although craniopharyngioma variants cannot be diagnosed based on imaging, the absence of calcifications, spherical shape, and the prevalence of solid components over cystic components favour the papillary variant [49].

Treatment

Craniopharyngiomas are benign tumours classified as grade I tumours according to WHO. Due to their locally aggressive growth, the infiltration of hypothalamic structures, and optic chiasm, their treatment is complicated and often burdensome for patients.

The diagnosis of craniopharyngioma is an indication for surgery. However, the lesion has a 65% recurrence rate. Most recurrences are observed in the first 10 years after surgery, although they may occur as many as 20 years after surgical treatment. In recurrent craniopharyngiomas or in prophylaxis of future recurrence of lesions without radical excision, radiotherapy or gamma-knife surgery may prove effective.

Currently, high hopes are pinned on targeted therapy. In 2015, Brastinos et al. [50] reported considerable regression of recurrent craniopharyngioma with dabrafenib plus trametinib — a combination of BRAF and MEK inhibitors, respectively. Thirty-five (35) days after initiating therapy, the tumour volume was reduced by 85%. Another important finding was a positive test result for the presence of BRAF V600E mutation in peripheral blood sample.

Intrasellar arachnoid cyst: primary empty sella syndrome

Epidemiology

Arachnoid cysts are rarely reported in literature. Between 1980 and 2007 only 51 cases with surgical treatment and confirmed histopathological diagnosis were described [51]. The mean age at diagnosis is 46 years [52].

Etiopathogenesis

Intrasellar arachnoid cysts are likely to develop as a consequence of wide aperture of the sellar diaphragm. Autopsies showed that only in 42% this opening is narrow enough to tightly encircle the infundibulum [53]. It was also demonstrated that the intrasellar space occupied by the pituitary decreases with age. Both these conditions result in sellar penetration by subarachnoid space filled with cerebrospinal fluid. The fluid is thus trapped within the sella as in a one-way valve effect [50]. Elevated intracranial pressure, observed in 50% of patients with primary empty sella syndrome, is also likely to play a role in the pathogenesis [54].

Clinical picture

Clinical symptoms associated with an arachnoid cyst are not particularly different from those observed in other cystic lesions. Arachnoid cysts, like other cysts, cause vision impairment, headache and — slightly less frequently — clinical symptoms of hypopituitarism. The latter most commonly include reduced libido, impotence, menstrual cycle disturbances, and difficulties with conception [50]. Clinically significant endocrine dysfunction usually affects 1–2 axes, although thorough endocrine assessment and pituitary stimulation tests may reveal anomalies in all pituitary axes. The most common finding is insufficiency of the gonadal axis. Furthermore, patients with intrasellar arachnoid cysts more commonly present with depression and obesity [55].

The coexistence of empty sella syndrome and pituitary adenoma has been described in literature [56, 57]. The coincidence of these two pathologies requires further studies. Additionally, some patients with an intrasellar arachnoid cyst present symptoms of depression with elevated ACTH levels, which indicates pseudo-Cushing's syndrome.

Diagnostic imaging

MRI findings are characteristic and, in most cases, allow for the differentiation between arachnoid cyst and pituitary adenoma. Isointensity or slight hyperintensity of the cyst against cerebrospinal fluid is a characteristic feature. Additionally, the lesion is balloon-shaped,

protrudes towards the suprasellar region, and modulates but does not infiltrate the medial wall of the cavernous sinus [29]. The pituitary stalk is usually clearly visible and shifted backwards.

Treatment

Neurosurgery is indicated in patients with clinical symptoms. The recurrence rate after surgical treatment is similar to that observed with Rathke's cleft cysts.

Secondary empty sella syndrome

Epidemiology

The incidence of secondary empty sella syndrome is unknown. Recently, it has been diagnosed more and more often due to the development of diagnostic techniques and new therapeutic options used for treatment of lesions located in the sellar-suprasellar region.

Etiopathogenesis

Secondary empty sella syndrome may be a consequence of pituitary adenoma apoplexy, neurosurgery, radiotherapy, or pharmacotherapy [58–60]. Lymphocytic hypophysitis and Sheehan's syndrome are rare causes of secondary empty sella syndrome.

Diagnostic imaging

Magnetic resonance imaging shows the picture of an empty sella. The pituitary gland is atrophic and its position within the sella is asymmetric. It pulls the stalk, which is shifted beyond the median line. The signs of displacement are not observed in secondary empty sella syndrome as appears from the absence of pituitary compression.

Clinical picture

Clinical symptoms depend on the size and activity of the adenoma in which the necrosis developed. A characteristic group of patients with empty sella syndrome includes patients with clinical symptoms of acromegaly with GH and IGF-1 levels falling within normal ranges. These are patients who recovered spontaneously from adenoma apoplexy. In some cases, necrosis of the tumour is not complete and the adenoma still shows some hormonal activity [61].

In cases of classic apoplexy, the incidence of hypopituitarism is high [62]. Additionally, higher risk of GH-oma and prolactinoma occurrence in a compressed pituitary has been described [63]. These lesions may remain undetectable on MRI.

Treatment

In patients with hypopituitarism, treatment is based on hormone replacement therapy.

Epidermoid cyst

Epidemiology

Epidermoid cysts are typically found in the cerebellopontine angle, although they may occasionally develop in the sellar-suprasellar region. They account for less than 1% of sellar-suprasellar cystic lesions [2].

Etiopathogenesis

Like in Rathke's cleft cysts and craniopharyngiomas, there are two hypotheses related to the development of epidermoid cysts. The first of them assumes a common origin of epithelial lesions from the remnants of the craniopharyngeal duct, while according to the second hypothesis, called the metaplastic theory, these lesions develop as a consequence of the transformation of intrasellar space epithelium triggered by an inflammatory process.

Clinical picture

Epidermoid cysts produce symptoms associated with increased intracranial pressure — mainly headache, and with the compression of optic chiasm, such as impairment of visual acuity and restricted vision field [64]. Cases of pituitary apoplexy were also reported in patients with epidermoid cyst located in the sellar-suprasellar region.

Diagnostic imaging

MRI typically shows a hyperintense lesion in T1- and T2-weighted images.

Treatment

Surgery is the only effective method of treatment. Due to the adherence of epidermoid cyst to nervous structures, complete resection is often impossible, hence epidermoid cysts recur in 25% of cases.

Xanthogranuloma

Epidemiology

Xanthogranulomas are very rare lesions of the sellar-suprasellar region. In professional literature on the subject published in English, only a few dozen cases have been described to date.

Etiopathogenesis

The theories of the aetiopathogenesis of xanthogranulomas are the same as the ones of epidermoid cysts.

Clinical picture

Typical symptoms of cholesterol granulomas include headache and vision impairment. Patients with xanthogranuloma may develop panhypopituitarism.

Table I. ***Clinical symptoms, endocrine dysfunction and characteristic features on MRI of cystic lesions located in the sellar-suprasellar region***

Cystic lesion	Most common clinical symptoms*	Endocrine dysfunction	Intensity and characteristic features on MRI
Rathke's cleft cyst	Headache, visual field impairment, secondary amenorrhea, impotence, reduced libido	Insufficiency of all axes is possible, hyperprolactinemia Possible coexistence of adenoma, most commonly GH-oma, ACTH-oma, rare diabetes insipidus	Located in intermediate lobe, with largest diameter — usually < 20 mm, various intensity: usually hypointense in TI-weighted imagesTI and hyperintense in T2-weighted images, nodule inside the cyst "an egg in a shell" image
Craniopharyngoma	Headache, visual field impairment, secondary amenorrhea, obesity, impaired memory, circadian rhythm disorders, polyuria, polydipsia	Insufficiency of all axes is possible, hyperprolactinemia, diabetes insipidus (sometimes masked or adipsic DI)	Various intensity of the lesion, size of the lesion is usually > 20 mm, calcifications within the lesion, wall enhancement following contrast administration**, compression of the 3rd ventricle floor structures, solid-cystic components
Intrasellar arachnoid cyst	Headache, visual field impairment, loss of libido, infertility, secondary amenorrhea, depression	Insufficiency of all hormonal axes, often subclinical	Isointense against cerebrospinal fluid, balloon-shaped lesion protruding towards the suprasellar region
Secondary empty sella syndrome	Rare, dependent on the pathogenesis of cyst	No endocrine dysfunction, hyperpituitarism, hypopituitarism	The same as in intrasellar arachnoid cyst
Epidermoid cyst	Headache, vision impairment	Possible hypopituitarism	Picture varies The lesion is usually hyperintense
Cholesterol granuloma	Headache, vision impairment	Possible hypopituitarism in a few axes	Differentiation from other cystic lesions is not possible

*not ranked by frequency
**also possible in inflammatory Rathke's cleft cyst

Diagnostic imaging

Cholesterol granuloma cannot be differentiated from Rathke's cleft cyst or craniopharyngioma on MRI [65].

Treatment

Surgery relieves the symptoms of increased intracranial pressure. A low recurrence rate of xanthogranulomas has been observed in case studies reported so far. In patients with symptomatic hypopituitarism, replacement therapy should be started.

Summary

Patients with cystic lesions of the sellar-suprasellar region require in-depth hormone testing and long-term observation of several years' duration. It is important to rule out hypopituitarism and the co-existence of a pituitary adenoma that is undetectable on magnetic resonance imaging. In some cases, preoperative diagnostic tests are inconclusive, and it is only postoperative histopathological examination with the use of immunohistochemical staining among other methods that leads to the final diagnosis. Table 1 shows clinical symptoms, endocrine dysfunction, and diagnostic imaging used for lesions located in the sellar-suprasellar region.

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