

## MANAGEMENT OF ENDOCRINE DISEASE

## Pituitary ‘incidentaloma’: neuroradiological assessment and differential diagnosis

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## Abstract

Pituitary incidentalomas are a by-product of modern imaging technology. The term ‘incidentaloma’ is neither a distinct diagnosis nor a pathological entity. Rather, it is a collective designation for different entities that are discovered fortuitously, requiring a working diagnosis based on the input of the radiologist, endocrinologist and often a neurosurgeon. In addition to pathological conditions affecting the pituitary gland, a thorough knowledge of the radiological characteristics of normal variants and technical artifacts is required to arrive at an accurate differential diagnosis. After careful radiological and hormonal evaluation, the vast majority of pituitary incidentalomas turn out to be non-functioning pituitary microadenomas and Rathke’s cleft cysts (RCCs). Based on the low growth potential of non-functioning pituitary microadenomas and RCCs, periodic MRI surveillance is currently considered the optimal management strategy. Stricter follow-up is required for macroadenomas, as increases in size occur more frequently.

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## Introduction

New diagnostic and therapeutic methods influence medicine in many positive ways. However, besides the obvious benefits they also have some unintended consequences. Modern radiological investigations are no exception. High-resolution imaging provides the opportunity to visualize anatomical structures more clearly. On the other hand, it increases the number of findings that are unrelated to the reason for the original

scan. Hence, it is a challenge to know what to do when faced with such ‘diseases of modern technology’ that are often termed incidentalomas.

The term ‘incidentaloma’ can be applied to a random discovery in any organ. In everyday clinical practice, incidentalomas are most frequently found in kidneys, thyroid gland, liver, adrenal glands and pituitary gland. However, incidentalomas of endocrine glands present

## Invited Author’s profile

**Dr Albert Beckers**, MD PhD is the Chief of the Department of Endocrinology at the University Hospital Centre, Liège and Full Professor at the University of Liège, Belgium. He oversees a department with multiple clinical and research areas of interest, including pituitary tumors, thyroid disease, genetic causes of endocrine cancers and rare inherited syndromes. Dr Beckers has authored a highly regarded series of digital projects on pituitary disease and has published more than 250 original articles in prestigious peer-reviewed journals. His research for which he received the 2016 Geoffrey Harris Prize, includes the original characterization and description of the syndrome, familial isolated pituitary adenomas (FIPA), and a newly described pediatric syndrome X-linked acrogerism (X-LAG).



additional challenges not only for their high prevalence, but also for the risk of autonomous hormonal activity or for impairing normal glandular function. As frank clinical manifestations are characteristically absent, resolving the true hormonal status of incidentalomas may be challenging. Recent progress in neuroimaging has resulted in increased recognition of sellar and parasellar lesions. In order to be termed as a pituitary incidentaloma, the imaging investigation should be performed in patients without overt signs and symptoms of pituitary disease. Pituitary adenomas and Rathke's cleft cysts (RCCs) are the most frequently encountered incidentally discovered entities in the pituitary region. However, the differential diagnosis of an incidentally discovered sellar mass is much broader and includes a large number of other entities (Table 1) (1).

**Table 1** Differential diagnosis of pituitary incidentalomas.

Anterior pituitary tumors
Pituitary adenoma
Pituitary hyperplasia
Pituitary carcinoma
Posterior pituitary tumors
Pituicytoma
Granular cell tumors
Benign parasellar tumors
Meningioma
Craniopharyngioma
Neurinoma
Lipoma
Malignant tumors
Glioma
Germ cell tumor
Primary lymphoma
Chordoma
Chondrosarcoma
Chondroma
Ependymblastoma
Plasmocytoma
Pituitary metastases
Malformative lesions
Rathke's cleft cyst
Dermoid cyst
Epidermoid cyst
Arachnoid cyst
Hamartoma
Inflammatory and granulomatous lesions
Lymphocytic hypophysitis
Granulomatous hypophysitis
Langerhans cell histiocytosis
Tuberculosis
Sarcoidosis
Pituitary abscess
Vascular lesions
Aneurysms
Cavernous angiomas
Cavernous sinus thrombosis

The aim of this review is to discuss the differential diagnosis of pituitary incidentalomas from the radiologist's and endocrinologist's perspectives.

### How frequent are pituitary incidentalomas?

Data on the prevalence of pituitary incidentalomas is generally derived from retrospective autopsy and imaging studies. The estimated figures vary widely from 1.5 to 38% depending on the era of the study and the study population. This variability reflects differences in definitions of pituitary incidentaloma used by the authors (asymptomatic, non-functioning pituitary adenoma or incidentally noted lesion); the type of the study (autopsy or radiological) and the imaging technique (CT, 1.5 T or 3.0 T MRI) (2, 3).

In the largest meta-analysis of autopsy studies comprising 18 902 examined pituitaries from 32 series, the mean prevalence of pituitary incidentaloma was 10.7% (range 1.5–31%) (2). Lesions were uniformly distributed between sexes and among adult age groups. Importantly, the prevalence of macroadenomas in autopsy series is <1% (2). Some studies report slightly increased prevalence in the elderly population (4, 5). Kastelan and Korsic suggested that an age-related decline in peripheral hormonal secretion could lead to compensatory feedback stimulation of gonadotropic cells, thereby stimulating the early stages of pituitary tumor development (4).

The radiological prevalence of incidentalomas in the sellar and parasellar regions has increased with technological advances (6, 7, 8, 9, 10). Earlier studies were performed using CT, which is considered less sensitive than MRI for detecting lesions of the pituitary. Pituitary incidentalomas detected during PET have also been reported in clinical case studies and in retrospective series of patients with cancer (11, 12, 13, 14, 15). MRI studies in unselected populations report micro-incidentaloma rates of 10–38% (16, 17). Similar to autopsy series the percentage of macroadenomas is quite low: 0.2% in CT series (18) and 0.16–0.3% in MRI studies (19, 20). These data derived from normal populations or apparently asymptomatic patients are in contrast with the prevalence of clinically relevant pituitary adenomas, which is closer to 1 case per 1064–1200 (21, 22). It is clear that few of the incidentally discovered microadenomas in pathology and radiology series progress to macroadenomas (2, 3). The proportion of macroadenomas, however, is higher in some neuroradiological series, where imaging was performed in patients with non-specific symptoms/signs

(23, 24, 25, 26). In the largest series of incidentally discovered pituitary lesions, imaging was performed most often for investigation of headache (40%). Other indications included trauma, cerebrovascular accidents or transient ischemic attacks, sinusitis, cervical spine disorders, visual loss, and syncope (23, 25, 27, 28).

Currently MRI is the modality of choice for detailed assessment of the majority of pituitary lesions, while CT has a supplementary role mainly for its advantages in the evaluation of changes in bone structure of the sella and calcifications (29). The increasing use of high-field MRI allows for multiplanar high contrast images of the pituitary and its adjacent structures. Noise artifacts inherent to high-resolution scanning may pose additional challenges when interpreting acquired images.

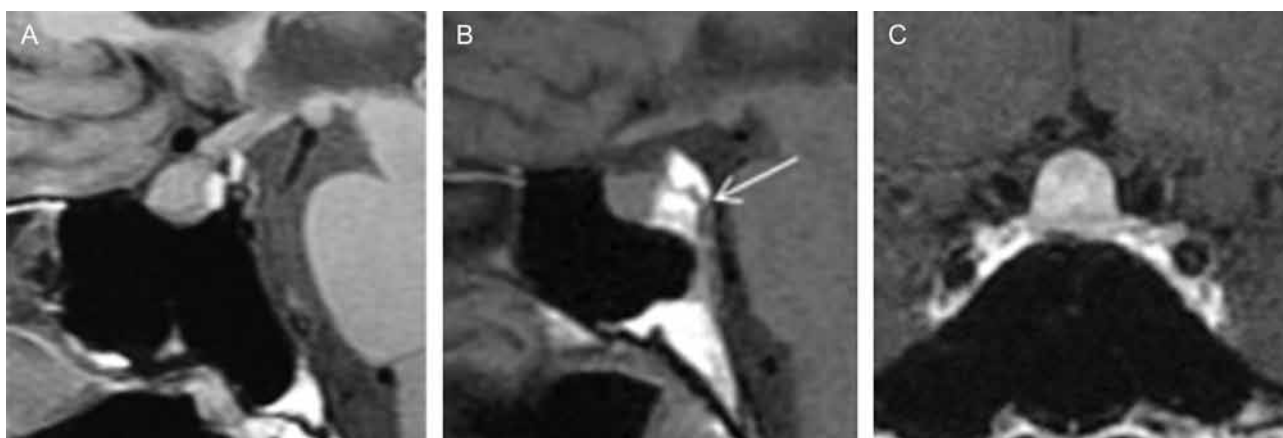
### Pitfalls in pituitary imaging

While individual practices vary from center to center, pituitary MRI studies usually include pre-contrast T1-weighted and T2-weighted spin-echo coronal and sagittal sections with thin slices. Coronal and/or sagittal T1-weighted spin-echo gadolinium-enhanced images are also often acquired. In order to gain the maximum amount of clinically useful information, the following items should be obtained: use of high matrix size (512), coronal spin-echo T1-weighted and fast spin-echo T2-weighted images, sagittal and axial T1-weighted images (to fully evaluate the posterior pituitary), and careful use of gadolinium contrast agents (30). Properly performed

volumetric assessments can be helpful for follow-up of lesion progression, but these are often not performed in the routine setting when a sellar lesion is discovered by chance. While not used routinely, axial sequences can be of significant additional use in the differential diagnosis of certain sellar lesions. Diagnostic pitfalls can be avoided by using pulse sequences adapted for the sella and by recognizing artifacts such as magnetic susceptibility, partial volume, chemical shift or pulsatility. Occasionally some incidental findings may be variants of the normal pituitary.

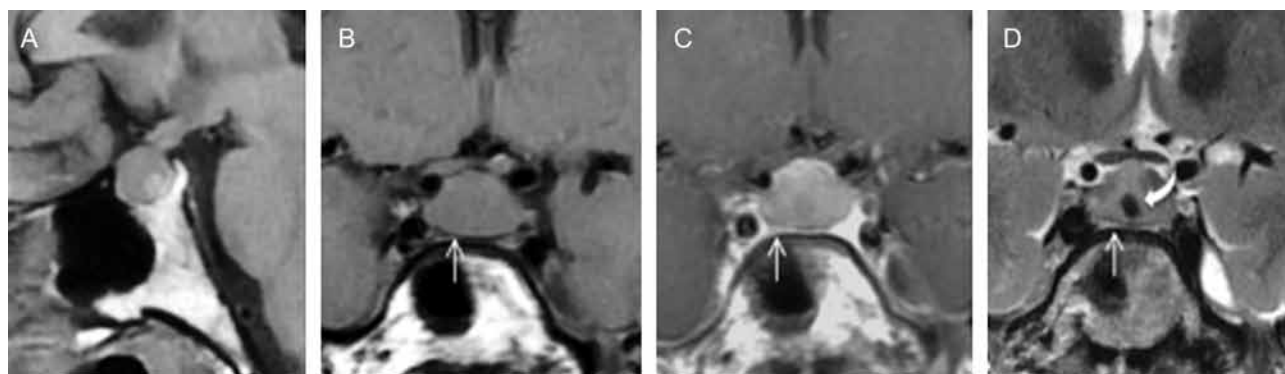
### The small sella

The inter-individual variability of the size of the sella turcica sometimes produces a pseudoenlargement of the pituitary on images where a normal-sized pituitary is visualized in a relatively small sella (31, 32). This normal anatomical variant can be mistaken for an enlargement of the content of the pituitary fossa and can lead to an incorrect diagnosis of a pituitary mass such as isointense pituitary adenoma or 'pituitary hyperplasia'. In adults, hyperpneumatization of the sphenoid sinus may be associated with a small sella since the pneumatization of the sinus may limit the depth of the pituitary fossa. In such cases the pituitary gland may project beyond the sellar aperture. A thick dorsum sellae, either pneumatized or consisting of fat and bone, can decrease the anteroposterior pituitary fossa diameter. Furthermore, in adolescent females the presence of a small or narrow sella



**Figure 1**

Small sella. Sagittal T1-weighted images show (A) small or flat sella, extensive pneumatization of sphenoid sinus, and a bulging normal pituitary gland; and (B) small sella and thick dorsum sellae (arrow). Coronal T1-weighted image after contrast enhancement shows marked upward bulging of the normal pituitary gland with extensive sphenoid sinus pneumatization and a narrow sella in an adolescent girl (C).



**Figure 2**

Enlarged pituitary content of multiple origins in a female with intracranial hypotension after failed lumbar puncture. Sagittal (A) and coronal (B) T1-weighted, coronal T1-weighted contrast-enhanced (C) and coronal T2-weighted (D) images reveal a large T1-isointense RCC with an intracystic T2-hypointense nodule (curved arrow) associated with an enlarged inferior coronary sinus (thin arrows).

can increase the physiological convexity of the pituitary (Fig. 1). Therefore, in cases of an enlarged pituitary gland with normal T1 and T2 signals and normal enhancement after gadolinium injection, a small sella should be considered in the differential diagnosis. The degree of the pneumatization of the sphenoid sinus, the shape of the dorsum sellae and the width of the sella should also be taken in account. Other possible conditions that may be associated with upward convexity of the pituitary gland include isointense holosellar pituitary adenoma and an isointense Rathke's cleft cyst which are infrequent (Fig. 2). Although rare, the volume of a normal-sized sella can also be reduced by an unusually large inferior coronary sinus, a sellar spine or a medial deviation of the internal carotid arteries ('kissing' carotid arteries) or trigeminal arteries (Fig. 3).

### Physiological and secondary pituitary enlargement

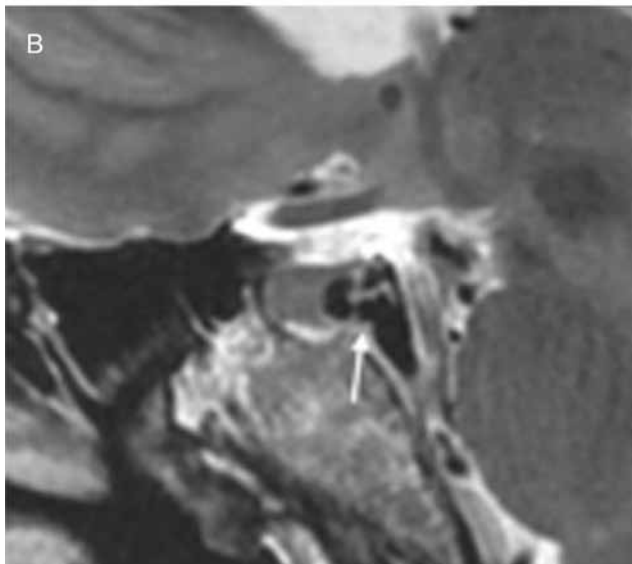
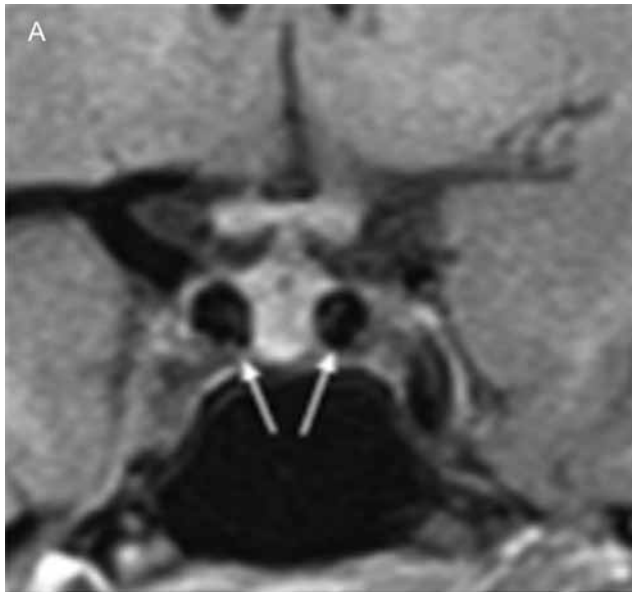
Another incidental finding on neuroimaging is an increase in pituitary size following physiological hypertrophy of pituitary cells (33). A number of imaging studies of healthy volunteers reported sex-dependent and age-dependent variations in size and contour of normal pituitary. In up to half of young women the superior pituitary contour is convex, although the size of the pituitary rarely (0.5%) exceeds 9 mm (34, 35, 36, 37). The increase in height of the normal pituitary, generally observed in younger women, could be due to age-related changes of the hypothalamic–pituitary–gonadal axis (38, 39). Lactotroph hyperplasia during pregnancy, thyrotroph hyperplasia due to severe primary hypothyroidism or

pituitary hyperplasia due to hypersecretion of releasing hormones (corticotropin-releasing hormone and growth hormone-releasing hormone) should also be ruled out when such diffuse pituitary abnormalities are revealed on MRI (Fig. 4) (40, 41, 42, 43). Recent reports suggest that a lack of sex hormone feedback might induce development of pituitary hyperplasia in Klinefelter syndrome (44).

### Technical artifacts

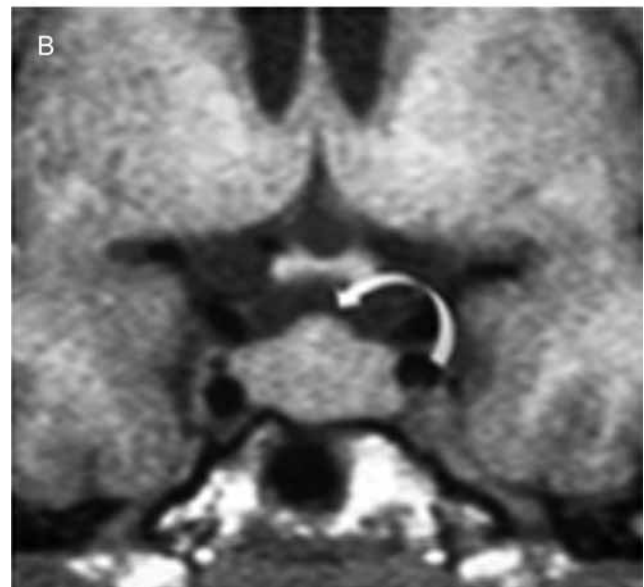
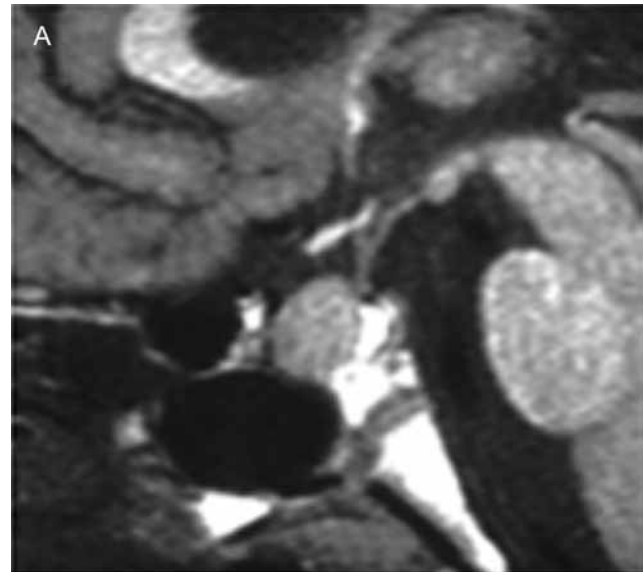
A number of artifacts may complicate the correct interpretation of sellar and parasellar MRI (30). They can easily mimic intrasellar lesions, in particular pituitary microadenomas. Partial volume artifacts occur when a 3 mm thick cut includes parts of different anatomical structures, such as anterior pituitary gland and sphenoid sinus anteriorly, dorsum sellae posteriorly, or intracavernous internal carotid arteries laterally. In such cases the average intensity of the different components of the cut section calculated by the computer can simulate an intrasellar tumor. Partial volume effects can be eliminated by coupling orthogonal projections or by using 1 mm thick cuts. Magnetic susceptibility artifacts are responsible for geometrical distortion and localized signal intensity changes at the interface between anatomical structures with different signal intensities, predominantly in the case of a curved interface. Magnetic susceptibility artifacts are often present at the level of the sellar floor and are more pronounced on 3.0 T MRI, but these can be accounted for with technical adjustments. Chemical shift artifacts and ghosting are related to the high signal of fat. They can compromise the visualization



**Figure 3**

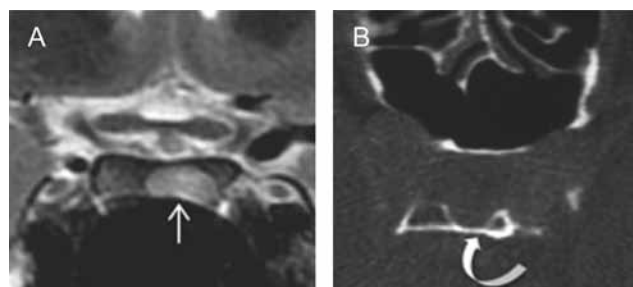
Vascular anomalies narrowing the sellar content. 'Kissing' internal carotid arteries (arrows) on coronal T1-weighted image (A). Trigeminal artery piercing the dorsum sella on sagittal T2-weighted image (B).

of the storage of vasopressin in the posterior lobe on axial T1-weighted sections when the dorsum sellae is fatty, particularly on 3.0 T MRI. Fat saturation techniques can be useful in such cases. A prominent posterior lobe and its fossula hypophyseos sometimes can be mistaken for a posteriorly located pituitary adenoma on coronal T2-weighted images (Fig. 5). The topography of the posterior lobe itself, which is beyond the midline in

**Figure 4**

Primary hypothyroidism in a 9-year-old girl. Regular enlargement of a homogeneous pituitary gland on sagittal (A) and coronal (B) T1-weighted images (upward convexity of the pituitary is shown with arrow).

about half of cases, is readily visualized on non-enhanced axial T1-weighted images. Flux artifacts arise mainly due to pulsating internal carotid arteries and cerebrospinal fluid. They are more severe on 3.0 T MRI and can blur or pollute the pituitary fossa or the subarachnoid spaces. All of these artifacts should be considered when clarifying the nature of incidental lesions in order to avoid possible mistakes in diagnosis.



**Figure 5**

Posterior lobe mimicking a pituitary lesion on coronal T2-weighted image (arrow) (A). Deep fossula hypophyseos on axial CT (B).

### Determining the nature of pituitary incidentalomas

Pituitary adenomas and Rathke's Cleft cysts (RCCs) are the most common entities in patients with pituitary incidentalomas and account for up to 90% of all lesions (6, 27, 28, 45). Other etiologies are less frequent – other tumors, mostly craniopharyngiomas in 4.2–5.6% and cystic malformations in 2.9–5.2% (46, 47, 48). It should be noted that these figures come generally from surgical series since definitive diagnosis is only possible after histopathological examination. The proportions of the two most common entities – pituitary adenomas and RCCs – also depend on the localization of the lesions. In cases of suprasellar lesions adenomas predominate, while RCCs are more common among intrasellar lesions.

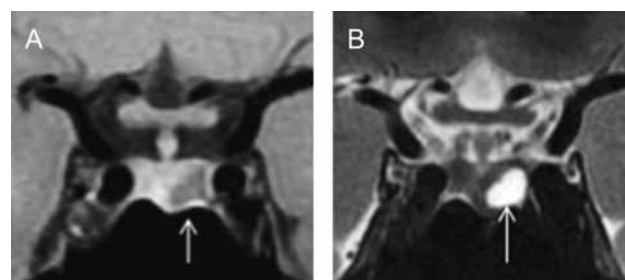
The majority of incidental pituitary adenomas are small clinically non-functioning tumors. Secreting adenomas usually present with clinical symptoms of hypersecretion that facilitate their diagnosis, although subtle hormonal changes may not be clinically evident. In a recent study, 77% of incidentally discovered pituitary adenomas were found to be non-functioning, 18% were prolactinomas and 3% were growth hormone secreting; the prevalences of different secretion patterns may be biased by the study population and the reason for pituitary imaging (28). Many large series of pituitary incidentalomas exclude hyperfunctioning adenomas and the overall prevalence of different secretory types is, therefore, not well established. Moreover, some patients with hypersecreting pituitary tumors discovered incidentally have clinical manifestations that were unrecognized at the initial examination (25). Such incidentally found functioning adenomas are usually prolactinomas. Unsuspected acromegaly can be revealed in some cases of pituitary incidentalomas (28, 49).

Subclinical Cushing's disease occurred in about 4% of histologically confirmed incidentaloma cases. Systematic screening for hypercortisolism and silent adrenocorticotrophic hormone (ACTH)-secreting tumors should be considered at the time of identification of a pituitary incidentaloma (50).

Distinguishing pituitary adenomas from other non-adenomatous lesions may be quite challenging. However, there are some radiological characteristics that may provide clues to the diagnosis.

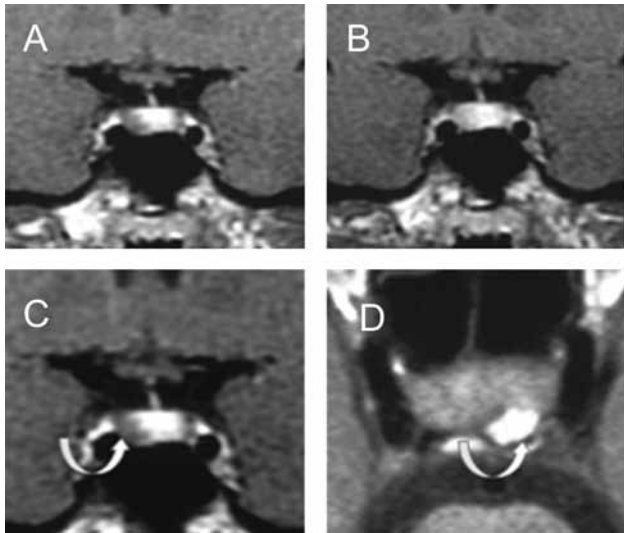
### Solid lesions

The differential diagnosis of a solid mass in the sellar regions should start with a pituitary adenoma. There may be areas of necrosis and hemorrhage with different signals on T1-weighted and T2-weighted sequences (51). In cases of cavernous sinus invasion, the internal carotid artery is usually unaffected (51). Intrasellar microadenomas (<10 mm) have some specific characteristics: lateralization inside the adenohypophysis, possible deformation of the sellar diaphragm and displacement of the pituitary stalk. Classically, microprolactinomas appear hypointense on T1-weighted images and hyperintense on T2-weighted sequences (Fig. 6), while many GH-secreting microadenomas can be isointense or hypointense on T2-weighted sequences (46). The enhancement after contrast injection is often minimal. About 5–10% of microadenomas are discovered exclusively on post-contrast images (30, 51, 52). Dynamic imaging with contrast is not always useful and may cause false-positive results. In 50% of normal glands, the posterior pituitary is off the midline (JF Bonneville, Personal Communication). If only the early phase of dynamic imaging is considered (when only the posterior pituitary but not the adenohypophysis is enhanced), this can falsely mimic a pituitary adenoma (Fig. 7).



**Figure 6**

Microprolactinoma. The adenoma (arrows) is T1-hypointense (A) and T2-hyperintense (B) on coronal images.

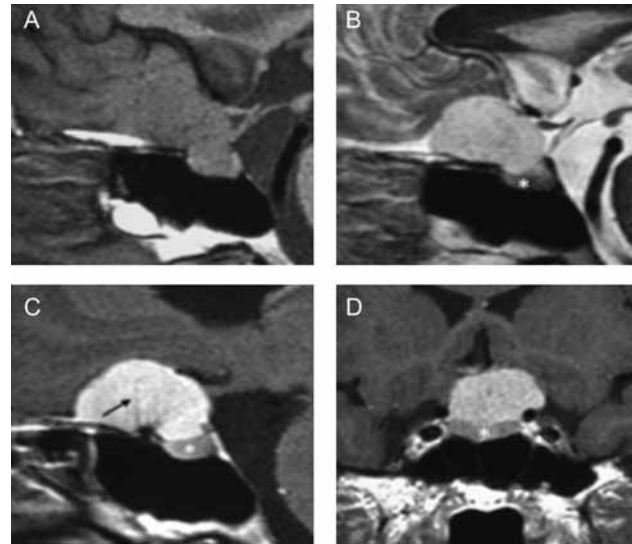


**Figure 7**

Normal dynamic imaging (A, B and C). Panel (C) shows magnification of normal delayed enhancement of the anterior pituitary simulating a pituitary adenoma (arrow). Panel (D) shows normal off-midline location of the posterior lobe (arrow) on an axial T1-weighted image.

Meningiomas are the second most common solid tumors in the pituitary region. They arise from the arachnoid cells of the dura and can often mimic the clinical picture of non-functioning pituitary adenomas with headache, visual disturbances and hypopituitarism (53). Their imaging characteristics, however, often can them to be distinguished from other sellar lesions (54). They usually do not enlarge the size of the sella and normal pituitary tissue can be visualized under the tumor. Meningiomas are isointense in T1-weighted images and hyperintense in T2-weighted images and tumor enhancement is intense and homogeneous with a linear thickening of the dura called the 'dural tail' (Fig. 8) (47). The internal carotid artery is often compressed when the meningioma invades the cavernous sinus (55). Substantial narrowing of the carotid lumen resulting in cerebrovascular insufficiency is, however, a rare event (56).

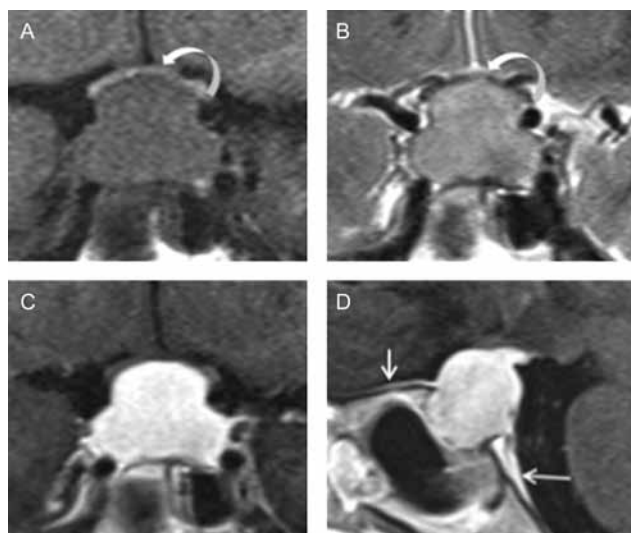
Tumors arising from the neurohypophysis like pituicytoma and granular cell tumors must also be considered when assessing intrasellar masses (48, 53). These lesions are usually isointense compared with gray matter in T1 and sometimes displace the normal adenohypophysis anteriorly. Although originating from the posterior lobe or the infundibulum, these tumors rarely cause diabetes insipidus. Taking into account that about 5–10% of germ cell tumors are found both in



**Figure 8**

Presellar meningioma. Sagittal T1-weighted (A) and T2-weighted (B) sequences and contrast-enhanced T1-weighted sagittal (C) and coronal (D) images demonstrate a meningioma inserted on the planum sphenoidale (arrow). It has stronger enhancement than the pituitary gland (marked with asterisk).

the suprasellar and pineal regions, the finding of such bifocal lesions can aid in the differential diagnosis. The suprasellar region is sometimes the origin of malignant primary brain tumors like gliomas originating from the optic tract/hypothalamus (46, 48, 57). Primary CNS lymphomas have also been described in the parasellar region (58). Malignant tumors, however, seldom remain silent for long and usually present with compression symptoms, hypopituitarism and diabetes insipidus. Their detection as an incidental finding would be extremely fortuitous. Some solid malignant tumors, especially breast and lung carcinomas, have been reported to metastasize rarely to the pituitary region. Metastasis usually affects the posterior lobe and presents with diabetes insipidus. In patients with a known primary tumor, likely metastatic lesions are not considered incidental findings. However, while searching for brain dissemination of a primary cancer, other non-metastatic pituitary lesions are more likely to be detected. Such cases can present serious clinical difficulties because metastatic lesions are similar to pituitary adenomas in appearance. Some distinguishing features of metastasis, albeit non-specific, include loss of posterior lobe bright spot and thickening of the pituitary stalk, bone erosions, and invasion of the sellar diaphragm (46, 48). PET has also been suggested

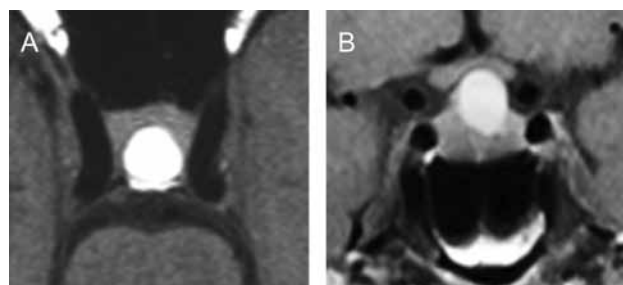


**Figure 9**

Lymphocytic hypophysitis. Coronal T1-weighted (A) and T2-weighted (B) sequences and contrast-enhanced T1-weighted coronal (C) and sagittal (D) images show enlarged sellar content abutting the optic chiasm (curved arrow). The lesion is T1-isointense, T2-hyperintense, and becomes markedly enhanced after gadolinium injection. The dural tail is shown with arrows.

as being useful to differentiate malignant from benign lesions. Positive PET findings can be consistent with malignant lesions rather than benign ones (59). There is a significant overlap, however, between the appearances of metastatic lesions, meningiomas and adenomas on PET images, hence caution should be used in their interpretation (13, 14, 60).

Chordomas and chondromas are rare bone-destroying tumors that arise from the primary notochord and cartilaginous remnants respectively (48). They can mimic invasive macroadenomas with inferior expansion (51). Occasionally the normal pituitary tissue can be distinguished above the tumor, which can help in its differentiation from invasive pituitary adenomas (61). Lymphocytic hypophysitis is another entity to be considered in the differential diagnosis of symmetric homogeneous enlargement of the pituitary. This autoimmune disorder usually affects women in the peripartum period and is characterized by frequent suprasellar extension, thickening of the stalk and intensive contrast accumulation (Fig. 9) (62, 63). Again, most of these conditions are associated with clinical symptomatology and would be exceptional findings if discovered fortuitously.



**Figure 10**

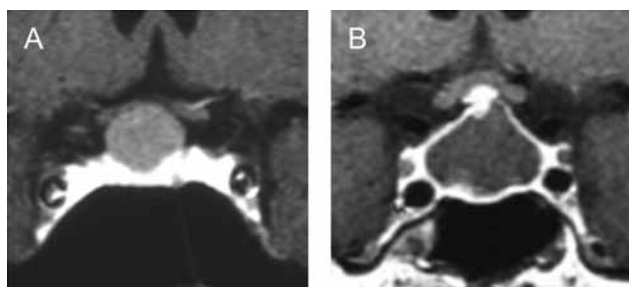
Mucoid T1-hyperintense RCC on axial T1-weighted image (A), located in the midline between the anterior and posterior lobes. A coronal T1-weighted image (B) shows an RCC on the upper surface of the pituitary, as an 'egg in an egg cup'.

### Cystic lesions

Incidentally found cystic lesions in the sellar and parasellar region need to be distinguished from a necrotic pituitary adenoma and non-pituitary entities such as RCCs, dermoid and epidermoid cysts, and cystic craniopharyngiomas. Necrotic macroadenomas usually lead to sellar enlargement and the walls of the tumor show distinct contrast uptake (51). A fluid level may be present in some cases.

RCCs are malformations that originate from the remnant of the squamous epithelium of Rathke's pouch and consist of a single layer of cuboidal or columnar epithelial cells filled with cystic components (64, 65). RCCs occur mostly in adults and usually are small and asymptomatic and as such they are the most common cystic pituitary incidentaloma and can be found in up to 22% at autopsy (46). Most of these lesions are intrasellar, but they can also lie on the sellar diaphragm, as 'an egg in an egg cup' (Fig. 10). They can expand above the sellar region and may become symptomatic causing compression of the optic tract or pituitary dysfunction. The basal MRI signal of RCC is highly variable and depends on the content of the cyst, which can be serous or mucinous (66). They are more frequently hyperintense on T1-weighted images. Characteristic of RCC are T2-hypointense intracystic nodules formed by cholesterol and are observed in 70% of T1-hyperintense RCC. Usually the cyst wall does not enhance after contrast administration, except in cases of complications such as infection, hemorrhage or rupture (Fig. 11) (64). Intrasellar RCCs cause no or limited mass effects, whereas pituitary adenomas may imprint the bony contours of the sella, compress the posterior lobe and displace the pituitary stalk.





**Figure 11**

RCC on coronal T1-weighted image after gadolinium injection. Panel (A) shows the usual pattern: the cyst wall is not enhanced. Panel (B) shows cyst wall enhancement of a complicated RCC.

About 50% of craniopharyngiomas occur in children and adolescents, but there is also another peak of occurrence in the elderly (67). They arise from squamous cells of the remnants of Rathke's pouch and can be predominantly cystic, predominantly solid or mixed in nature. Calcifications are present in two-thirds of all cases and in almost all cases in children (68). Although craniopharyngiomas are benign tumors, they usually have an aggressive behavior and a tendency to infiltrate (69). Hence, they rarely remain asymptomatic and most commonly present with headache, visual disorders, hypopituitarism and diabetes insipidus. In children, however, these symptoms may not be recognized initially and diagnosis can be delayed (67). The appearance on MRI varies depending on the proportion of solid and cystic components, the presence or absence of calcification, and the contents of the cyst (70). The solid portion of craniopharyngiomas usually appears isointense or hypointense on T1-weighted and hyperintense on T2-weighted sequences. The cystic part is hyperintense on T1-weighted sequences with a thin contrast-enhancing rim (71). Although calcifications are not specific, they are very characteristic of a craniopharyngioma (46, 72, 73, 74, 75). In all patients with an incidentally discovered pituitary lesion and a suspicion of a craniopharyngioma, both MRI and CT should be performed to establish a definitive diagnosis.

Dermoid and epidermoid cysts are other lesions that often arise in the midline in the sellar and parasellar region. They include epithelial elements resulting from incomplete separation of the neuroectoderm from the cutaneous ectoderm (48). Their imaging characteristics are non-specific and their differentiation from other cystic lesions may be difficult. Dermoid cysts usually contain fat

components and are heterogeneous on T1 images and hyperintense on T2 images (46, 65, 76). Epidermoid cysts contain keratin and are almost identical in appearance to cerebrospinal fluid with no contrast enhancement (65). Arachnoid cysts are rare herniations of the arachnoid diverticulum through the sellar diaphragm and can be intrasellar or suprasellar (76). On MRI they appear as well-defined lesions that are isointense to cerebrospinal fluid on T1-weighted and T2-weighted sequences and are not enhanced by gadolinium (74).

### To treat or not to treat?

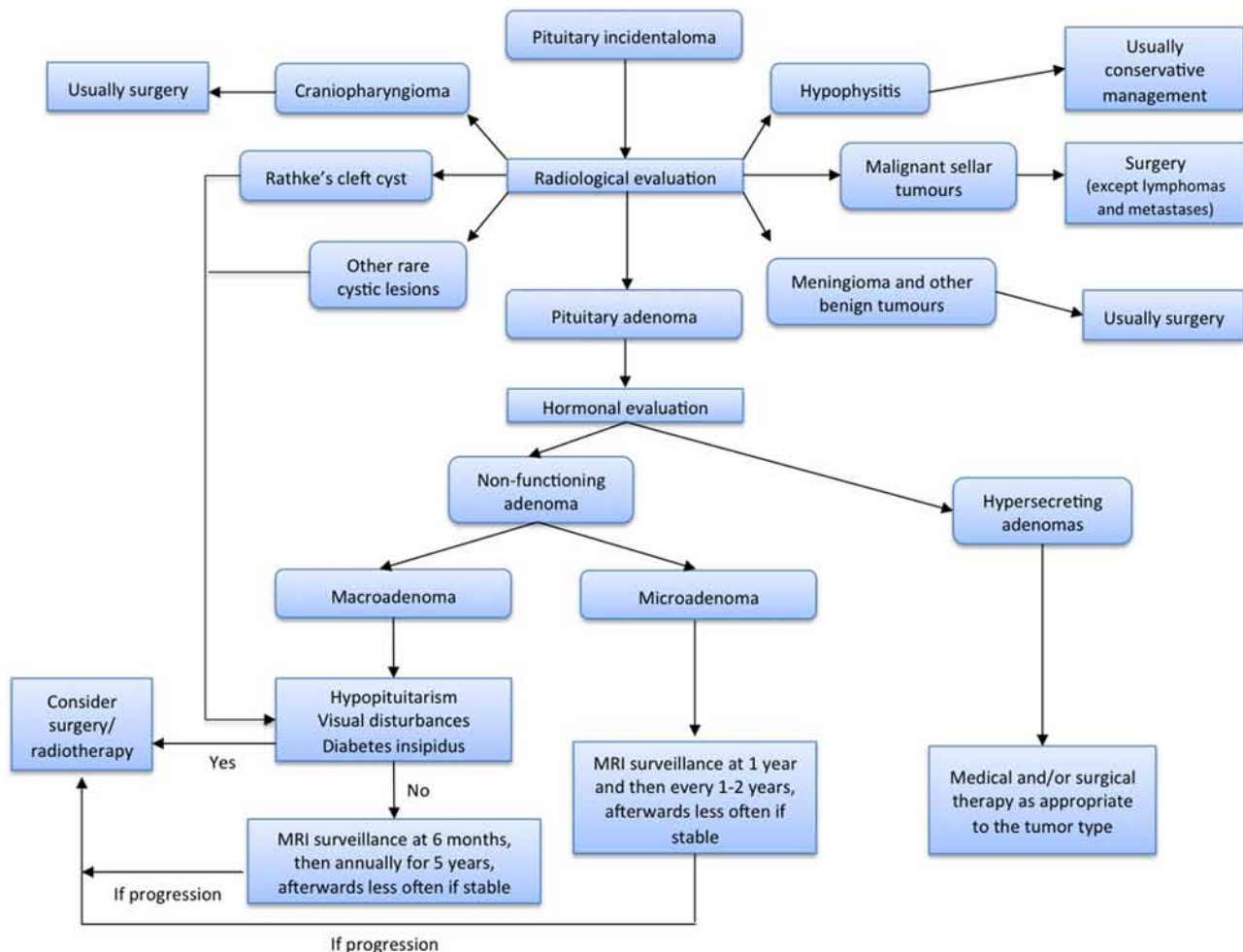
Once a pituitary incidentaloma has been discovered and a differential diagnosis made, the clinician is faced with a decision about what to do. The management of incidentally found sellar lesions depends on the suspected nature of the tumor (pituitary adenoma, RCC, craniopharyngioma, etc.), its size and clinical symptomatology (visual and neurological disorders), and hormonal status (hyposecretion/hypersecretion/normal secretion). Thorough clinical examination should be performed for signs and symptoms of hypersecretion or hyposecretion that may have been overlooked, followed by hormonal evaluation. Close attention to normal and physiological variations and technical artifacts can help to avoid unnecessary surgical interventions. Neurosurgery remains the treatment of choice for many secreting and non-secreting pituitary lesions causing visual abnormalities due to compression of optic chiasm and signs of tumor mass effect. Diabetes insipidus occurs infrequently in pituitary adenomas, whereas it is a common clinical manifestation associated with other pituitary lesions, particularly pituitary metastases (77). The age of the patients and their general health status are important issues that need to be considered when deciding the treatment strategy.

Medical therapy with dopamine agonists and somatostatin analogs can produce tumor shrinkage in the case of prolactinomas and acromegaly respectively, which may provide important clinical improvements. Usually surgical referral is also indicated in many of other lesions in the sellar and parasellar regions like meningiomas, craniopharyngiomas and other less frequent tumors as well as large cysts when these cause compression symptoms. Infiltrative lesions, however, like lymphocytic and granulomatous hypophysitis are largely managed conservatively, except when symptoms are severe or progressive – in such cases surgery may

be performed or corticosteroids may be used. (63, 78, 79, 80) Primary lymphomas in the region are managed with chemotherapy and radiotherapy and rarely surgically, although stereotactic biopsy may be needed for accurate diagnosis (61).

As the vast majority of pituitary incidentalomas are non-functioning pituitary adenomas and most of these are microadenomas, the decision about their management is determined by their growth potential. The behavior of incidentally found pituitary adenomas has been studied by a number of separate groups worldwide (25, 49, 81, 82, 83, 84). Based on the current data regarding the natural history of small incidentally discovered non-functioning adenomas, watchful waiting is considered the most appropriate strategy (1). The growth potential of non-functioning pituitary adenomas is heavily dependent on their size at diagnosis, with larger tumors

having greater growth potential. In a systematic review and meta-analysis, Fernandez-Balsells and coworkers reviewed the natural history of incidentalomas and non-functioning pituitary adenomas (85). In a group of 11 studies (patient number ranged from 50 to 289 per study), the authors reported a higher incidence of tumor growth in macroadenomas and solid lesions as compared with microadenomas and cystic lesions (85). Macroadenomas and microadenomas had incidences of tumor growth of 12.53 and 3.32 per 100 patient-years respectively. Although data quality was poor (due to small numbers of studies with heterogeneous designs), macroadenomas had a significantly higher incidence of new endocrine dysfunction (11.9 per 100 patient-years) and visual field worsening (0.5 per 100 patient-years), as compared with microadenomas (85). In other detailed reviews, tumor enlargement occurred in 10%



**Figure 12**  
Flowchart for decision making in the management of pituitary incidentaloma.

of microadenomas, with tumor reduction seen in 6% during 2.5–8 years of observation (2). In contrast, tumor growth in macroadenomas can occur in up to 24% of cases (2, 73).

The development and worsening of clinical symptoms such as visual disturbances and the occurrence of apoplexy directly depend on tumor size and most frequently occur in growing tumors (2, 10, 85, 86, 87), although visual loss may be reversible in most cases (83, 88, 89). Macroadenomas are also the usual cause of hypopituitarism in patients with pituitary incidentalomas (28). The presence of partial or panhypopituitarism varies greatly in published series (0–41% of macroadenomas) (1, 2). In cases of significant growth of pituitary adenomas during follow-up or the development of compression symptoms such as visual field defects and vision abnormalities, surgical treatment must be strongly considered (1). Although surgery can improve hypopituitarism, further worsening of hypopituitarism due to surgery itself may occur.

Cystic lesions increase in size less frequently than solid tumors (85). During follow-up, 20% of 115 non-functioning adenomas enlarged over the course of 10–173 months, while only 5.3% of 94 probable RCCs increased in size. Furthermore, more than 50% of tumors that decrease in size are cystic (25). Thus, many RCCs and other cystic lesions may stay stable without growth and might be safely followed up with careful laboratory and radiological evaluation (1, 90).

The duration and periodicity of radiological follow-up also depends on tumor nature and size. Current consensus guidelines recommend performing a follow-up MRI 6 months after the initial incidental discovery for macroadenomas and after 1 year the discovery for microadenomas. When no tumor growth is observed, MRI should be repeated annually for macroadenomas and every 1–2 years for microadenomas for the next 3 years and less frequently afterward, if no growth occurs. Others have even suggested that no surveillance needs to be implemented for non-functioning microadenomas <5 mm in size, although this approach could miss the rare lesions that expand aggressively (51). Baseline hormonal evaluation is warranted, both to establish whether any clinically relevant endocrine change is present at diagnosis, and to provide a yardstick to assess any change overtime. In asymptomatic patients with incidentally found microadenomas, the costs of evaluation can be significant. While data are not widely available for different countries, the US experience suggests the initial evaluation costs >6000 US dollars per patient (not including follow-up assessments) (91).

Cost containment will require improved understanding of the growth potential of pituitary incidentalomas and adherence to existing guidelines/recommendations to avoid unnecessary expenses in long-term follow-up, particularly of chronically stable small lesions (1).

For accurate follow-up evaluation of pituitary incidentalomas, particularly non-functioning adenomas, the question of MRI reproducibility is significant. Ideally, the follow-up analysis should be performed at the same clinical center, using the same imaging protocols for more precise and easier comparison with previous images.

## Conclusions

Increased availability of high-quality neuroimaging techniques has led to a rise in the detection of incidental pituitary lesions, and their evaluation is becoming more common in everyday endocrine practice. In the case of a fortuitously discovered sellar or parasellar lesion, the initial workup should be focused on distinguishing pathological conditions from normal or physiological variants. A suggested diagnostic pathway is outlined in Fig. 12. Since imaging characteristics provide valuable clues for the differential diagnosis, close collaboration among specialists in radiology, endocrinology and neurosurgery is required. The majority of incidentally found pituitary lesions turn out to be non-functioning pituitary adenomas or RCCs and current data suggest that they can be managed conservatively in most cases by periodical MRI monitoring allied with simple clinical surveillance. Large or growing lesions, or pituitary lesions associated with hormonal or local symptoms, require active and regular follow-up by multidisciplinary treatment teams.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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