Silent Corticotroph Adenomas

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Pituitary adenomas are uncommon tumors of the central nervous system. They can arise from any anterior pituitary cell type. Clinical manifestations of pituitary adenomas can be related to the-excessive secretion of their hormonal products, or can be clinically “silent”. Pituitary adenomas are classified based on the combination of immunocytochemistry, biochemical testing and clinical findings (1)

- **Classic**: Pituitary adenomas that secrete hormonal products in sufficient quantities to cause characteristic signs and symptoms related to the hormone excess.
- **Subtle**: Pituitary adenomas that secrete hormonal products that produce mild clinical manifestations related to the hormone excess.
- **Clinically silent**: Pituitary adenomas that can be classified by immunocytochemistry and secrete hormonal products that can be detected by biochemical testing but do not cause clinical signs or symptoms.
- **Totally silent**: Pituitary adenomas that can be classified by immunocytochemistry as arising from a specific anterior pituitary cell type but do not secrete a sufficient amount of their hormonal products to affect the serum concentration or urine excretion.

Table 1. type of silent pituitary adenoma based on immunocytochemistry (1)

Adenoma Type	Immunostaining	Incidence
Null cell	None	
Gonadotroph	FSH, LH, α-subunit	43-64%
Thyrotroph	TSH	<1%
Corticotroph	ACTH	2.9-5.7%
Somatotroph	GH	9%
Lactotroph	Prolactin	1-2%
Plurihormonal	Multiple hormones	2%

Silent corticotroph adenoma

Silent corticotroph adenomas (SCAs), also named silent ACTH adenomas, are defined as pituitary adenomas showing positive staining for adrenocorticotrophic hormone (ACTH) in immunohistochemical studies, but are not associated with perioperative clinical or laboratory features of hypercortisolaemia(2). In 1978,

Kovacs et al (3) reported a case of SCA and were the first to propose this disease category. SCAs account for 1.1–6% of surgically removed pituitary adenomas and 17–22% of ACTH immunoreactive tumours(4-6). The sex predominance, as reported in neurosurgical series, remains unclear.

Pathology and pathogenesis

Currently, two distinct pathologic subtypes of SCAs are recognized (7). Macroscopically, both type 1 and type 2 SCAs are generally macroadenomas with variable invasion or compression of parasellar structures. This distinguishes them from typical Cushing's adenomas, which are mostly microadenomas at clinical presentation.

Type 1 SCA is histologically and ultrastructurally indistinguishable from classical Cushing's adenoma. It is densely granulated, basophilic on haematoxylin and eosin staining, periodic acid-Schiff (PAS)-positive, and shows strong ACTH expression by the majority of tumour cells. By contrast, type 2 adenoma is generally chromophobic or weakly basophilic with scattered PAS-staining and reveals only patchy or faint ACTH-positivity by immunohistochemistry.

Presenting clinical manifestations

SCAs typically present with local mass effects [headache (8.3–70.4%), visual deterioration (41.7–86.7%), cranial nerve palsies (7–18.5%), endocrine dysfunction (amenorrhoea, galactorrhoea, impotence: 11.1% — hypopituitarism: 26–33.3%)]. Acute or subacute pituitary apoplexy has been described in 9–41.7%. Other less commonly reported presenting clinical manifestations include loss of consciousness and nasal obstruction (8).

Most tumours are macroadenomas with suprasellar extension present in 87–100% of the cases. This is in contrast to Cushing's disease, which is mostly attributed to microadenomas. Sphenoid or cavernous sinus invasion has been reported in 30–52% and signs of haemorrhage, necrosis or cystic changes in 64% of the tumours. Notably, in a series of 23 cases of SCAs, there was no difference in the rates of invasion or apoplexy between subtypes 1 and 2 (7).

Treatment and prognosis

Surgery remains the main therapeutic approach. Based on data from 13 subjects with SCAs followed-up for at least 3 years, Scheithauer et al (7) found that persistent or recurrent pituitary tumours on sellar imaging was exhibited in 54% with no difference among subtypes 1 and 2. The recurrence in SCAs was more frequent than in non-functioning pituitary adenomas and tended to behave more aggressively.

Case series of 12 patients with silent corticotroph adenomas reported acute adrenal insufficiency in 2 patients after resection of their tumor, suggesting that they had secreted cortisol excessively preoperatively (6).

Several reports have described patients with known SCA who subsequently develop Cushing's disease. Baldeweg et al. (5) studied 22 cases during a mean observation interval of 4.8 years. In 4 cases, hypercortisolaemia was observed later in the course of the disease.

Medical treatment is not currently included in the therapeutic protocol of SCAs. A case of shrinkage of a recurrent tumour expressing D2 receptors following treatment with cabergoline has been reported (9) suggesting that the use of dopamine agonists may be an alternative option.

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