

Silent Corticotroph Adenomas

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ABSTRACT

Silent corticotroph pituitary adenomas (SCA) are defined as pituitary adenomas showing positive staining for adrenocorticotrophic hormone in immunohistochemical studies, but not associated with perioperative clinical or laboratory features of hypercortisolaemia. They account for 1.1–6% of surgically removed pituitary adenomas. Currently, two distinct pathologic subtypes of SCA are recognised. Their pathogenesis remains unclear. They present with local mass effects (headache, visual deterioration, cranial nerve palsies, endocrine dysfunction). The lack of manifestations of cortisol excess has not been conclusively explained. In surgical series, 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. Surgery remains the main therapeutic approach. Attempts to identify predictors of recurrence have not been successful. Management and follow-up protocols should be planned taking into account their potential aggressive behaviour, particularly upon recurrence. The development of florid pituitary Cushing's syndrome and local recurrence followed by metastatic disease (occasionally outside the central nervous system) have been rarely reported. **(Arq Bras Endocrinol Metab 2007;51/8:1314-1318)**

Keywords: Silent corticotroph adenomas

RESUMO

Adenomas Corticotróficos Silenciosos.

Adenomas corticotróficos silenciosos (ACS) são definidos como adenomas hipofisários que apresentam coloração positiva para o hormônio adrenocorticotrófico em estudos imuno-histoquímicos, mas não são associados com achados clínicos ou laboratoriais peri-operatórios de hipercortisolemia. São responsáveis por 1,1–6% dos adenomas hipofisários removidos cirurgicamente. Atualmente, dois subtipos patológicos distintos de ACS são reconhecidos, mas sua patogênese permanece obscura. Eles se apresentam com efeitos de massa local (cefaléia, deterioração visual, paralisia de nervos cranianos, disfunção endócrina). A ausência de manifestações de excesso de cortisol não é suficientemente explicada. Em séries cirúrgicas, a maioria dos tumores são macroadenomas com extensão supresselar, presente em 87–100% dos casos, em contraste com a doença de Cushing, que é principalmente atribuída a microadenomas. A cirurgia continua a principal ação terapêutica. A tentativa de se identificar preditores de recorrência tem sido mal sucedida. Protocolos de manejo e acompanhamento devem ser planejados levando-se em consideração o seu comportamento potencialmente agressivo, particularmente na recorrência. Raramente tem sido reportado o desenvolvimento de síndrome de Cushing hipofisária florida e recorrência local, seguida de doença metastática (ocasionalmente fora do sistema nervoso central). **(Arq Bras Endocrinol Metab 2007;51/8:1314-1318)**

Descritores: Adenomas corticotróficos silenciosos

Recebido em 04/10/07
Aceito em 10/10/07

SILENT CORTICOTROPH PITUITARY ADENOMAS (SCA) are defined as pituitary adenomas showing positive staining for adrenocorticotrophic hormone (ACTH) in immunohistochemical studies, but not associated with perioperative clinical or laboratory features of hypercortisolaemia. In 1978, Kovacs et al. (1) reported a case of SCA and were the first to propose this disease category. More detailed description followed by Horvath et al. in 1980 (2).

They account for 1.1–6% of surgically removed pituitary adenomas (2–5) and 17–22% of ACTH-immunoreactive tumours (4,6). The sex predominance, as reported in neurosurgical series, remains unclear. Thus, Webb et al. (7) suggested that it is more common in females (70.4%) whereas Scheithauer et al. (8) found a male/female ratio of 69.9/30.5.

PATHOLOGY AND PATHOGENESIS

More than in other pituitary adenomas, the diagnosis of SCA depends upon the correct interpretation of specific pathological features in the context of clinical and biochemical parameters during the perioperative period. Good communication between the pathologist and endocrine team is therefore important for making the diagnosis. Occasionally, patients with large macroadenomas and visual symptoms are referred to neurosurgery before full endocrine work-up is completed; if ACTH expression is demonstrated in such a tumour, a histopathological report of SCA should only be issued after the endocrine team has confirmed that relevant clinical and laboratory examinations were carried out and did not show any evidence of Cushing's disease.

Currently, two distinct pathologic subtypes of SCAs are recognised (8). A third type of SCA, initially proposed in 1980 (2), is now thought to be unrelated to the SCA spectrum and is simply referred to as "silent type 3 adenoma". 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, the type 2 adenoma is generally chromophobic or weakly

basophilic with scattered PAS-staining and reveals only patchy or faint ACTH-positivity by immunohistochemistry. Ultrastructurally, type 2 SCAs contain scattered, typically "tear-drop"-shaped neurosecretory granules, 200–400 nm in diameter (smaller than those of type 1 SCAs) and of variable electron density (6,9). Furthermore, type 2 SCAs lack abundant intermediate filaments in their cytoplasm compared with type 1 SCAs and the classical densely granulated Cushing's adenoma. This feature can be assessed immunohistochemically with cytokeratin antibodies such as Cam5.2. Electron microscopy is not always necessary to make the diagnosis of SCA; however, it is useful for distinguishing type 2 SCAs from null-cell adenomas with very rare ACTH expression or plurihormonal adenomas where ACTH expression is accompanied by an unusual combination of other anterior pituitary hormones.

In both SCA subtypes, ACTH is usually the only immunohistochemically detectable anterior pituitary hormone. However, in a study of 12 cases, scant co-expression of prolactin was found in 6/8 type 1 and 2/4 type 2 SCAs (6); an earlier study found some prolactin positivity in 2/23 cases (8). Interestingly, a few patients harbouring silent-corticotroph and prolactin-producing "double-adenomas", likely clonally distinct, have been reported (6). This, together with the presence of scattered prolactin-producing cells within a proportion of typical SCAs may suggest a potential pathogenetic link (6,8) between SCAs and neoplastic transformation of prolactin-producing cells. A paracrine dopamine antagonistic effect of beta-endorphin, a proopiomelanocortin (POMC) derivative produced by SCAs, on lactotroph cells may play a role in this process.

SCAs may often show pathological evidence of previous regressive change in the form of cholesterol clefts, haemosiderin deposition and fibrosis (4,7). This may appear on imaging as cystic change, suggesting in some instances an alternative preoperative diagnosis of craniopharyngioma (6).

If residual anterior gland is available for examination, Crooke's hyaline change in non-neoplastic corticotrophs, a reliable indicator of recent hypercortisolaemia, is absent. Interestingly, rare SCAs with Crooke's hyaline change in the neoplastic cell population have been reported (10). This may either indicate hypersensitivity to physiological cortisol levels due to glucocorticoid receptor overexpression by these cells, or indeed suggest that some SCAs are only intermittently silent (see below) and not entirely independent from feedback-inhibition.

The pathogenesis of SCAs remains unclear. It has been suggested that presumed SCA precursor cells represent a distinct subtype of POMC-producing cells residing mostly in the vestigial *pars intermedia* of the human pituitary (11). Corticotroph cells in this anatomic location may lack the ability to respond to cortisol excess with Crooke's hyaline change (11), suggesting that they are biologically distinct. The pituitary-restricted transcription factor TPIT, specific for all POMC-lineage derived cells in the human pituitary (12), could be demonstrated in four out of five SCAs together with the POMC-transcript (12). It is therefore likely that the specific deficit responsible for the clinical silence in SCA tumour cells relates to abnormal processing of POMC to biologically non-functional ACTH molecules rather than aberrant lineage differentiation which may be related to a deficit in key POMC-processing enzymes, such as prohormone convertase 1 (see below). Alternatively, neoplastic cells in SCAs may harbour a pool of functional ACTH but are unable to release it due to galectin-3 deficiency or other defects in the neurosecretory pathway (13). Indeed, differential expression of galectin-3 can be used to distinguish functioning (galectin-3-positive) from non-functioning (galectin-3-negative) corticotroph tumours (14).

PRESENTING MANIFESTATIONS (clinical, biochemical, imaging)

SCA 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%)] (2,4-7). Acute or subacute pituitary apoplexy has been described in 9–41.7% (5-7). Other less commonly reported presenting clinical manifestations include loss of consciousness and nasal obstruction (5).

They are considered a separate entity from cyclical Cushing's disease, in which the biochemical evidence of hypercortisolaemia is detected intermittently in the course of the illness. The lack of manifestations of cortisol excess (despite the occasionally found elevated serum ACTH levels) has not been, as yet, conclusively explained and the molecular mechanisms underlying clinical silence are likely to be heterogeneous and dynamic. Proposed hypotheses include defective packaging of ACTH into secretory granules due to an inadequately developed Golgi complex, secretion of biologically inactive hormones, increased

intracellular degradation of hormones and the presence of morphologically similar, but functionally different parent cell type deriving from the *pars intermedia* that processes POMC differently (1,2,8,15-17). Notably, it has been shown that, in contrast to adenomas obtained from patients with Cushing's disease, which demonstrate strong positive prohormone convertase 1/3 (the enzyme involved in the post-translational processing of POMC into ACTH) immunoreactivity, silent corticotroph adenomas exhibit very weak expression (18).

In surgical series, most tumours are macroadenomas with suprasellar extension present in 87–100% of the cases (5-8). This is in contrast to Cushing's disease, which is mostly attributed to microadenomas (8). Sphenoid or cavernous sinus invasion has been reported in 30–52% (5,7,8) and signs of haemorrhage, necrosis or cystic changes in 64% of the tumours (8). 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 (8).

TREATMENT AND PROGNOSIS

Surgery remains the main therapeutic approach. The published reports on the prognosis of SCAs are limited consisting of series of 13–28 patients. Based on data from 13 subjects with SCA followed-up for at least 3 years, Scheithauer et al. (8) found that persistent or recurrent pituitary tumours on sellar imaging was exhibited in 54% with no difference among subtypes 1 and 2. In a series of 27 patients treated at the University of Virginia and followed-up for a median period of 60 months (range 3–254), Webb et al. (7) reported tumour recurrence in 37% (41.7% of those who did not receive post-operative radiotherapy, 33.3% of those who had radiotherapy after re-operation for residual tumour and 0% of those who had radiotherapy after first surgery). Two subjects (7.4%) experienced multiple recurrences (despite postoperative radiotherapy in one case), each of which was treated with re-operation. Among 22 patients, in whom the primary diagnosis of SCA was made, 23% developed recurrence. Interestingly, 40% of those who initially presented with recurrent tumours developed recurrences after treatment at the University of Virginia. Following comparison with historical data, the authors suggested that recurrence in SCAs was more frequent than in non-functioning pituitary adenomas, whereas the rate was similar to that for ACTH-secreting macroadenomas. Baldeweg et al. (5) studied 15

cases during a mean observation interval of 4.8 years (range 11 months–11 years). Recurrence was detected in 33.3% of the patients (in 66.7% of those who received and in 11.1% of those who did not receive post-operative radiotherapy). Two patients showed progression despite further treatment and both died of their pituitary tumour due to space occupying effects. Change to a more aggressive phenotype with evidence of an increased mitotic rate compared with the initial pathology was detected in a number of recurrent lesions. Finally, Bradley et al. (19) in a series of 28 patients with tumours expressing ACTH followed-up for a mean period of 5.8 years (range 1–16), reported tumour re-growth rate of 32.1%. The comparison of the outcome of 20 of the above patients who did not receive radiotherapy postoperatively with previously published data on 60 subjects with ACTH-immunonegative non-functioning pituitary adenomas (also not offered adjuvant radiotherapy) suggested no difference in the recurrence rates. In contrast to the ACTH immunonegative adenomas, none of which showed more than one episode of regrowth, two subjects with SCA experienced very aggressive tumour regrowth with multiple recurrences (one patient had three operations and two courses of radiotherapy for two episodes of recurrence and a second one had four operations, two courses of radiotherapy and gamma knife therapy after three recurrences in total) suggesting that ACTH immunopositive adenomas behave more aggressively.

Attempts to identify predictors of recurrence have not been successful. Thus, pre-operative tumour invasiveness, cavernous sinus extension, or dural invasion, tumour subtype, degree of ACTH immunoreactivity and Ki-67 index do not seem to be associated with increased risk of recurrence (5,7,19).

Notably, initial studies of classical markers of growth potential, such as mitotic count and nuclear expression of the proliferation-associated antigen Ki-67, showed no difference from functioning corticotroph adenomas (5,8). However, a more recent assessment of p53 oncoprotein expression and ploidy revealed a significantly higher presence of p53 and hypertetraploidy in SCAs than functioning corticotroph adenomas (20).

The development of florid pituitary Cushing's syndrome has been rarely reported (5,21-23). The implicated pathophysiological mechanisms remain uncertain; changes in the cellular processing enzymes or POMC mRNA leading to production of functional ACTH molecules has been speculated as one of them (24).

Local recurrence followed by metastatic disease (occasionally outside the central nervous system) has been also rarely described (3). The latency period between resection of the primary lesion and the presentation of metastases ranges between 3–180 months. The malignant tumours may or may not be associated with the development of Cushing's disease (3,25). In a report of five cases of silent corticotroph carcinomas of the adenohypophysis, three of the primary tumours were indistinguishable from benign SCA. The remaining two were initially diagnosed as atypical adenomas showing nuclear pleomorphism, prominent nucleoli, mitotic activity, high MIB-1 labeling indices and p53 overexpression. The comparison of this series with 35 cases of Cushing's disease associated pituitary carcinomas suggested similar latency interval and survival (3). Notably, it has been proposed that the presence of Crooke's hyaline change in neoplastic cells of SCAs as well as functional corticotroph adenomas (so-called "Crooke's cell adenomas") has been associated with an aggressive phenotype (26), in rare cases potentially leading to pituitary carcinoma (3).

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 (27) suggesting that the use of dopamine agonists may be an alternative option; further trials are needed to investigate this hypothesis.

CONCLUSIONS

Nearly 30 years after the initial description of SCAs, they remain a challenging and enigmatic entity. Their pathogenesis and the factors determining their course are likely to be heterogeneous and dynamic. Management and follow-up protocols should be planned taking into account their potential aggressive behaviour, particularly upon recurrence.

REFERENCES

1. Kovacs K, Horvath E, Bayley TA, Hassaram ST, Ezrin C. Silent corticotroph cell adenoma with lysosomal accumulation and crinophagy. A distinct clinicopathologic entity. *Am J Med* **1978**;64:492-9.
2. Horvath E, Kovacs K, Killinger DW, Smyth HS, Platts ME, Singer W. Silent corticotrophic adenomas of the human pituitary gland: a histologic, immunocytologic, and ultrastructural study. *Am J Pathol* **1980**;98:617-38.
3. Roncaroli F, Scheithauer BW, Young WF, Horvath E, Kovacs K, Kros JM, et al. Silent corticotroph carcinoma of the adenohypophysis: a report of five cases. *Am J Surg Pathol* **2003**;27:477-86.

- Sahli R, Christ ER, Seiler R, Kappeler A, Vajtai I. Clinicopathologic correlations of silent corticotroph adenomas of the pituitary: report of four cases and literature review. **Pathol Res Pract** 2006;202:457-64.
- Baldeweg SE, Pollock JR, Powell M, Ahlquist J. A spectrum of behaviour in silent corticotroph pituitary adenomas. **Br J Neurosurg** 2005;19:38-42.
- Lopez JA, Kleinschmidt-Demasters Bk B, Sze CI, Woodmansee WW, Lillehei KO. Silent corticotroph adenomas: further clinical and pathological observations. **Hum Pathol** 2004;35:1137-47.
- Webb MK, Laurent JJ, Okonkwo DO, Lopes MB, Vance ML, Laws ER. Clinical characteristics of silent corticotrophic adenomas and creation of an internet-accessible database to facilitate their multi-institutional study. **Neurosurgery** 2003;53:1076-108.
- Scheithauer BW, Jaap AJ, Horvath E, Kovacs K, Lloyd RV, Meyer FB, et al. Clinically silent corticotroph tumors of the pituitary gland. **Neurosurgery** 2000;47:723-9.
- Thapar K, Horvath E, Kovacs K. Neoplasms of the sellar region. In: McLendon RE, Rosenblum MK, Bigner DD (eds). **Russell and Rubinstein's Pathology of Tumors of the Nervous System**. London: Hodder Arnold, 2006. pp. 663-764.
- Roncaroli F, Faustini-Fustini M, Mauri F, Asioli S, Frank G. Crooke's hyalinization in silent corticotroph adenoma: report of two cases. **Endocr Pathol** 2002;13:245-9.
- Horvath E, Kovacs K, Lloyd R. Pars intermedia of the human pituitary revisited: Morphologic aspects and frequency of hyperplasia of POMC peptide immunoreactive cells. **Endocr Pathol** 1999;101:55-64.
- Vallette-Kasic S, Figarella-Branger D, Grino M, Pulichino AM, Dufour H, Grisoli F, et al. Differential regulation of proopiomelanocortin and pituitary-restricted transcription factor (TPIT), a new marker of normal and adenomatous human corticotrophs. **J Clin Endocrinol Metab** 2003;88:3050-6.
- Jin L, Riss D, Ruebel K, Kajita S, Scheithauer BW, Horvath E, et al. Galectin-3 expression in functioning and silent ACTH-producing adenomas. **Endocr Pathol** 2005;16:107-14.
- Thodou E, Argyrakos T, Kontogeorgos G. Galectin-3 as a marker distinguishing functioning from silent corticotroph adenomas. **Hormones (Athens)** 2007;6:227-32.
- Reincke M, Allolio B, Saeger W, Kaulen D, Winkelmann W. A pituitary adenoma secreting high molecular weight adrenocorticotropin without evidence of Cushing's disease. **J Clin Endocrinol Metab** 1987;65:1296-300.
- Nagaya T, Seo H, Kuwayama A, Sakurai T, Tsukamoto N, et al. Pro-opiomelanocortin gene expression in silent corticotroph-cell adenoma and Cushing's disease. **J Neurosurg** 1990;72:262-7.
- Braithwaite SS, Clasen RA, D'Angelo CM. Silent corticotroph adenoma: case report and literature review. **Endocr Pract** 1997;3:297-301.
- Ohta S, Nishizawa S, Oki Y, Yokoyama T, Namba H. Significance of absent prohormone convertase 1/3 in inducing clinically silent corticotroph pituitary adenoma of subtype I — immunohistochemical study. **Pituitary** 2002;5:221-3.
- Bradley KJ, Wass JA, Turner HE. Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours but do not recur more frequently. **Clin Endocrinol (Oxf)** 2003;58:59-64.
- Scheithauer BW, Gaffey TA, Lloyd RV, Sebo TJ, Kovacs KT, Horvath E, et al. Pathobiology of pituitary adenomas and carcinomas. **Neurosurgery** 2006;59:341-53.
- Gogel EL, Salber PR, Tyrrell JB, Rosenblum ML, Findling JW. Cushing's disease in a patient with a 'nonfunctioning' pituitary tumor. Spontaneous development and remission. **Arch Intern Med** 1983;143:1040-2.
- Vaughan NJ, Laroche CM, Goodman I, Davies MJ, Jenkins JS. Pituitary Cushing's disease arising from a previously non-functional corticotrophic chromophobe adenoma. **Clin Endocrinol (Oxf)** 1985; 22:147-53.
- Cooper ME, Murray RM, Kalnins R, Woodward J, Jerums G. The development of Cushing's syndrome from a previously silent pituitary tumour. **Aust N Z J Med** 1987;17:249-51.
- Lloyd RV, Fields K, Jin L, Horvath E, Kovacs K. Analysis of endocrine active and clinically silent corticotrophic adenomas by in situ hybridization. **Am J Pathol** 1990;137:479-88.
- Farrell WE, Coll AP, Clayton RN, Harris PE. Corticotroph carcinoma presenting as a silent corticotroph adenoma. **Pituitary** 2003;6:41-7.
- George DH, Scheithauer BW, Kovacs K, Horvath E, Young WF Jr, Lloyd RV, et al. Crooke's cell adenoma of the pituitary: an aggressive variant of corticotroph adenoma. **Am J Surg Pathol** 2003;27:1330-6.
- Petrossians P, Ronci N, Valdés Socin H, Kalife A, Stevenaert A, Bloch B, et al. ACTH silent adenoma shrinking under cabergoline. **Eur J Endocrinol** 2001;144:51-7.

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