

N°2 Cushing's Syndrome Newsletter

September 2008

The Cushing's Syndrome Newsletter is a half-yearly publication reporting on a number of recent important events and provides up-to-date information on Cushing's Syndrome and Adrenal Cortical Carcinoma, published by John-Libbey-Eurotext. © 2008.



Introduction

The 90th annual meeting of the Endocrine Society was held in San Francisco, USA, on June 15-18, 2008. A record number of over 7400 clinicians and researchers working in the field of endocrinology attended the meeting. During the meeting, there were several presentations on Cushing's syndrome and adrenocortical cancer.

We present some of the main highlights below.

The Year in adrenal

■ Dr Young, Mayo Clinic, Minnesota, USA, presented the top 14 articles addressing the most important clinical questions and having the biggest influence on the diagnosis and treatment of adrenal disorders. A panel of experts chose these 14 from 185 articles of interest published this year. Among the top 14 papers, there were 5 publications on

« **A panel of experts chose these 14 from 185 articles of interest published this year.** »

adrenocortical cancer or Cushing's syndrome: **1/** adjuvant treatment for adrenocortical carcinoma, Terzolo et al, NEJM 2007; 356: 2372. **2/** Mutation in PDE8B, a cyclic AMP-specific phosphodiesterase in adrenal hyperplasia, Horvath et al, NEJM 2008; 358: 750. **3/**

Iodometomidate for Molecular Imaging of Adrenocortical Cytochrome P450 Family 11B Enzymes, Hahner et al, JCEM 2008; 93: 2358. **4/** Late recurrences of Cushing's disease after initial successful transsphenoidal surgery, Patil et al, JCEM 2008; 93: 358. **5/** The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline, Nieman et al, JCEM 2008; 93: 1526.

In Short

- Management of Adrenal incidentomas with sub-clinical Cushing's syndrome remains controversial.
- A future study will explore the potential of urine steroid profiling in the follow-up of patients with ACC.
- Physicians should be aware of the possibility of cyclic disease activity at initial diagnosis as well as after treatment during the follow-up period of Cushing's disease.
- Testing for Cushing's syndrome is recommended after excluding exogenous glucocorticoid use in patients with multiple and progressive symptoms suggestive of the syndrome and in patients with adrenal incidentaloma.

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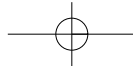
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The 90th annual meeting of the Endocrine Society



Management of adrenal incidentaloma

■ Dr Terzolo, Turin, Italy, discussed the issue in a meet the professor session. Adrenal incidentalomas occur more often in older people, and thus present a public health challenge of increasing importance. For this heterogeneous condition, different algorithms have been proposed; however, the clinicians working in the field who attended the session felt that these algorithms are not known well enough to everybody and thus are not in widespread use. Finding a significant pathology, such as overt hormone overproduction and/or primary adrenal malignancy provides a clear framework for diagnostic and therapeutic follow-up. However, diagnosis and management of subclinical Cushing's syndrome remains controversial, since there is no consensus on a gold standard for diagnosis and treatment. For screening, an NIH consensus in 2002 proposed the 1-mg dexamethasone suppression test with the traditional threshold of 5 µg/dL (138 nmol/L) to define adequate suppression. Lower cortisol values were discussed, however, the cutoff of 1.8 µg/dL (50 nmol/L) cannot be measured by all assays and test specificity decreases. Some experts recommend at least 2 abnormal concomitant tests to diagnose subclinical Cushing's syndrome. Although an increased frequency of the manifestations of the metabolic syndrome has been described in these patients, the management of the condition is still empirical and lacks prospective data. Thus, either adrenalectomy or conservative medical treatment of the metabolic syndrome have been suggested as treatment options.

outcome as a primary prognostic factor makes the skills of the surgeon very important for patients with adrenocortical carcinoma (ACC), and therefore, it was stressed that surgery on ACC patients should be centralized in specialized centers. Furthermore, the issue of open versus laparoscopic surgery was addressed in the German registry. 28 patients who had primarily laparoscopic operations - 10 of these operations had to be converted to an open procedure - and 28 matched controls were selected from the registry. The survival of the patients operated on laparoscopically was significantly better. These results should be interpreted knowing that surgeons very experienced in the field operated on these patients; the results could indicate that the skill of the surgeon is more important than the approach for the operation. Based on the survival data from the registry, a new staging system was proposed (ENS@T staging) with improved separation of overall survival between the groups: stage I: tumor < 5 cm, II: tumor > 5cm, III: tumor thrombus in renal vein/vena cava, or infiltration of adjacent tissue/organ, or positive lymph nodes, IV: distant metastasis. Examples for histological and molecular markers (Ki67, ERCC1 and Glut1) were presented with predictive value for overall survival or treatment response underlining the overall usefulness of the registry.



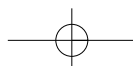
Treatment strategies in adrenal carcinoma

■ Dr Allolio, Würzburg, Germany, presented his views based on the German Adrenocortical Carcinoma Registry. Significantly, the follow-up analysis of the registry data provided clear cut evidence that the surgical outcome with respect to resection status is the main determinant of the patient's prognosis. The importance of the operation



Steroid profiling in the diagnosis and monitoring of adrenal cancer

■ Dr Art, Birmingham, UK, presented the results of the EURINE ACC study of ENS@T, which explored the value of steroid profiling by gas chromatography/mass spectrometry (GC/MS) in adrenocortical carcinoma (ACC). In ACC, a typical increase of excreted steroid precursors was found. Unsupervised bio-computational data analysis by machine learning techniques provided for a sensitivity of 82% and specificity of 97% in diagnosing ACC. Predictive and prognostic value will be refined and further evaluated in incidentalomas. Future study will explore the potential of urine steroid profiling in the follow-up of patients with ACC.



The Cyclicity of cortisol secretion in patients with Cushing's disease

Dr Alexandraki, London, UK, investigated retrospectively in a large series the cyclicity and variability of cortisol secretion in patients with Cushing's disease for a mean period of 14.8 years. In about 15% of cases, there was evidence of cyclic disease with a cycle duration of several years. According to this presentation, physicians should be aware of the possibility of cyclic disease activity at initial diagnosis as well as after treatment during the follow-up period. Cyclic disease was more prevalent in female patients.



Intravenous dexamethasone suppression test in the differential diagnosis of Cushing's syndrome

■ Dr Jung and coworkers, Fitzroy, Australia, presented retrospective data from 83 patients with endogenous hypercortisolism. An intravenous dexamethasone suppression test (1 mg dexamethasone per hour for 4 hours) had been performed and ACTH and cortisol were measured for two days. The ACTH and cortisol responses from these patients were compared with 30 age and BMI matched control subjects. While both ACTH and cortisol levels were readily suppressed upon IV dexamethasone in the control subjects, both ACTH and cortisol rebounded on day 2 after initial suppression in patients with pituitary Cushing's syndrome. In contrast, in patients with ectopic and adrenal Cushing's syndrome, cortisol levels were not suppressible during the observation period.

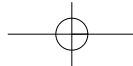
« *Partial suppression and hypercortisolism rebound on day 2 in Cushing's disease, no cortisol suppression in ACC and ectopic Cushing's syndrome.* »

Although the presented data were collected from a retrospective analysis and the number of patients with ectopic Cushing's syndrome was low, the intravenous dexamethasone suppression test might aid in the differential diagnosis of ACTH-dependent Cushing's syndrome.



Peri-operative ACTH levels upon surgery of ACTH secreting adenomas and prediction of long term outcome

■ Dr Abdelmannan, Cleveland, USA, evaluated the predictive value for the long term outcome of perioperative ACTH measurements in patients who underwent pituitary surgery for Cushing's disease. The prospective study included 55 patients with confirmed ACTH secreting pituitary adenomas. In this patient cohort, cortisol nadir was documented 18-24 hours post surgery, before glucocorticoid supplementation. Those patients (n=35) with undetectable serum cortisol levels were considered in remission. Nevertheless, within this subgroup, 5 patients developed clinical and biochemical recurrence after an observation period of up to 66 months. Interestingly, the minimal post-operative ACTH levels in the patients with long term recurrence were significantly higher in comparison to patients with long term remission. The findings of an ACTH level > 20 mg/L was associated with disease recurrence.



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Pathological diagnosis of adrenocortical carcinoma

■ At the present time adrenocortical carcinoma (ACC) suffers from an absence of reliable diagnostic criteria making adjuvant therapy trials and prognostic studies uncertain regarding the validity of their conclusions. Indeed, the most popular and valid diagnostic tool, Weiss score¹ is based on a set of nine pathological diagnostic criteria of equal weight (mitotic count > 5/10 HPF, atypical mitosis, nuclear grade III-IV, ≤ 25% clear cells, >1/3 diffuse architecture, necrosis, vascular invasion, sinusoid invasion, capsular invasion) which proper definition and reproducibly are still uncertain.

In 2001, a publication from Gicquel C² et al. confirmed a sensitivity of Weiss score of 95% but specificity around 50% using a cut off of three. In 2008, new molecular strategies have not yet been demonstrated that are superior to the Weiss score for ACC diagnosis³. For this reason, research in the area is still focussed on pathological score with the double aim of standardisation, including improved reproducibility, and also improved specificity. Recent publications are of interest in this regard. In 2002, Aubert S⁴. et al proposed a revised Weiss score based on five major criteria: (mitotic count > 5/10 HPF, atypical mitosis, ≤ 25% clear cells, necrosis, vascular invasion) based not only on diagnostic analysis of forty nine adrenal tumours but also on an analysis of reproducibility.

The diagnostic value of the revised Weiss score has been confirmed in a recent study⁵. However, a full definition of each parameter has still to be validated by all teams⁶. Regarding specificity of the diagnosis of ACC, analysis of mitosis looks appealing as demonstrated in a recent study⁷ which compared on an individual basis, various pathological criteria one by one. In this study⁷, they found the presence of atypical mitosis a specific criterion of malignancy as well as a mitotic count above or equal to 2 per 10 HPF (HPF = 5.232 mm²). These results should be related to studies^{8,9,10,11,12} that have demonstrated specificity above 90% of Ki67 index above 2.5 to 10%. While expecting soon a definitive standardisation of pathological criteria used for ACC diagnosis, combination of Weiss score and mitotic count assessment appears the best and simplest manner to perform an acceptable diagnosis of ACC in 2008.

1. Weiss L.M. et al. Am J Surg Pathol 1989
2. Gicquel C. et al. Cancer Res, 2001
3. Papotti et al. J Clin Pathol 2008
4. Aubert S. et al. Am J Surg Pathol 2002
5. van't Sant H.F. et al. Histopathology 2007
6. Papotti et al. J Clin Pathol 2008

7. Blanes A et al. Am J Clin Pathol 2007
8. Goldblum J et al. Modern pathol 1993
9. Gupta D. et al. App Immunohistochem and Mol Morphol 2001
10. Aubert S. et al Am J. Surg Pathol 2002
11. Stojadinovic Modern Pathol 2003
12. Schmitt A. et al. Histopathology 2006

Guideline for the diagnosis of Cushing's syndrome

Dr Nieman, NIH, Bethesda, USA, presented an overview on the Endocrine Society Clinical Practice Guideline for the diagnosis of Cushing's syndrome. These recently published (Nieman LK et al J Clin Endocrinol Metab. 2008 May;93(5):1526-40) guidelines were put together based on a systematic review of evidence from the literature. According to this guideline, testing for Cushing's syndrome is recommended after excluding exogenous glucocorticoid use in patients with multiple and progressive symptoms suggestive of the syndrome and in patients with adrenal incidentaloma. The urine cortisol, late night salivary cortisol and 1mg overnight or 2mg 48-hour dexamethasone suppression tests were recommended as initial tests with high diagnostic accuracy. Each test should be performed correctly and, if abnormal, should be substantiated with another test. Patients with concordant normal results were recommended not to undergo further evaluation unless there is a high clinical suspicion of endogenous hypercortisolism.

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