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EDITORIAL

Recent developments in the management of Cushing's syndrome☆

Novedades en el manejo del síndrome de Cushing

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Clinical suspicion of Cushing's syndrome (CS) is a complex challenge. To improve diagnosis of CS, analysis of facial images using computer techniques has recently been reported. One of the methods applies a semi-automatic analysis for nodes or benchmarks predefined as relevant in CS.[1] In a first publication comparing 20 women with CS to 40 control cases, matched by age only, the software achieved a total classification accuracy of 91.7%. However, this method does not work as well in a less restricted environment, and has several limitations: requires face and profile photographs, with strict head orientation requirements, and large sample sizes are required to adequately train the software.[2] Another group has used a deep learning approach for automatic identification of facial anomalies. This methodology, which has been shown to be helpful in diabetic retinopathy, can be trained with a small amount of data to provide a good outcome and only needs a frontal photograph, with no strict head orientation requirements. When applied to the clinical diagnosis of CS and acromegaly, it has a good precision and an acceptable level of sensitivity, with high specificity, as compared to the diagnosis made by medical staff. In addition, the regions of interest indicated by the algorithm agree with those indicated by the experts.[3]

A prospective analysis has shown that measurement of cortisol and cortisone in nocturnal salivary samples using liquid chromatography coupled with tandem mass spectrometry does not improve the sensitivity of testing nocturnal salivary cortisol (NSC) by enzyme immunoassay. This study shows the importance of testing more than one NSC sample, as most patients with one or more high levels do not have CS, and presence of only one high level implies poor specificity and a low positive predictive value. NSC levels may be very useful to exclude ACTH-dependent CS because two or more normal measurements allow for excluding it more than 95% of the time, and annual NSC testing could be of special value to detect recurrence of Cushing's disease (CD) after surgery. For adrenal CS, however, none of the methods for measuring steroids in saliva provide adequate sensitivity or positive predictive value.[4]

Hair cortisol measurement allows for retrospective testing of cortisol secretion in the previous weeks or months depending on the length of the hair analyzed, with potential value for diagnosis of cyclic CS. Various cut-off points with high sensitivity and specificity for the diagnosis of CS have been reported.[5,6] In addition, hair cortisol measurement may also show the natural history of the development of adrenal insufficiency.[5]

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Ceccato et al. stated that in the etiological diagnosis of CS, the CRH stimulation test is the cornerstone of differential diagnosis of ACTH-dependent CS: a basal cortisol level >743 nmol/L provides the greatest precision to diagnose an ectopic ACTH secretion syndrome (EAS), and presence of a marked percent increase (Δ%) in cortisol and ACTH levels suggests diagnosis of CD ($\Delta\%^{ACTH}$ 37% in EAS vs 229% in CD). In patients with CS who have adrenal masses and indeterminate basal ACTH levels, CRH testing is essential to discriminate etiology. As regards differential diagnosis of pseudo-CS, basal and stimulated ACTH and cortisol levels are lower in pseudo-CS, with similar percent increases in cortisol and ACTH levels. Basal cortisol and ACTH levels >444 mmol/L and 23 pg/mL respectively, and stimulated levels >685.5 nmol/L and 70 pg/mL respectively suggest diagnosis of CD.[7] With regard to this latter point, a review of pseudo-CS suggests that stimulation tests with dexamethasone-CRH or desmopressin continue to show no optimum cut-off points for the different clinical settings, and that none has become the gold standard for differentiating CS from pseudo-CS.[8]

The proposed composite approach including CRH stimulation tests and pituitary magnetic resonance imaging (MRI) followed by whole-body computed tomography (CT), with thin sections in cases where diagnosis of CD is not clear, is proposed as a non-invasive alternative for diagnosing ACTH-dependent CS. This approach has a 100% positive predictive value for CD in the event of a positive response to the stimulation test, both in patients in whom MRI shows an adenoma and in those with no MRI image and no tumor found in CT. Lack of response to tests, no adenoma image on MRI, and presence of ectopic tumor on CT has a 100% negative predictive value for CD. This noninvasive strategy would allow for avoiding petrosal sinus catheterization in 47% of cases in which it would have been recommended based on the classical algorithms for CS diagnosis, and represents a new approach in the diagnostic process of ACTH-dependent CS.[9] CRH stimulation may also be helpful for detecting by ^{18}fluorodeoxyglucose positron emission tomography (18F-FDG-PET) corticotropinomas not visualized with MRI, since stimulation with ovine CRH appears to increase radioisotope uptake and enhance visualization in late images.[10]

As regards drug treatment, the results of several clinical trials have been reported in the past year. Osilodrostat, an oral potent inhibitor of cytochrome P450 11B1 enzyme approved for the treatment of CS in the European Union, has been shown to rapidly decrease urinary free cortisol (UFC) levels in the LINC-3 trial. After 34 weeks of treatment, a greater proportion of patients maintained a complete response, defined as normalization of UFC levels, as compared to placebo (31 [86%] *vs* 10 [29%]; odds ratio 13.7 [95% CI 3.7–53.4]; $P < .0001$), as well as improvement in clinical signs and symptoms of hypercortisolism. The most common side effects reported include nausea (42%), headache (34%), fatigue (28%), and adrenal insufficiency (28%). Side effects due to accumulation of adrenal precursors are reported in 42% of patients.[11]

The results of the first prospective trial conducted with metyrapone to show its efficacy and safety in the treatment of patients with CS were presented in the European Congress of Endocrinology. UFC levels normalized in 23 of 48 patients with CS treated with metyrapone, with mean UFC and NSC reductions of 73.5% and 55% respectively, symptoms were normalized or improved, and quality of life improved after 12 weeks of treatment. The effect was marked after one week of treatment, with reductions in UFC and NSC levels by 49% and 36% respectively. The most common side effects include nausea (23%), decreased appetite (18%), fatigue (14%), adrenal insufficiency (12%), and headache (10%), with peripheral edema, hypokalemia or hypertension occurring in 6% of cases.[12]

Continuous intravenous infusion of etomidate, an imidazole derivative similar to ketoconazole, achieves rapid control in patients with severe hypercortisolism or in life-threatening situations. Administration of etomidate in critical care units using a standardized protocol is able to normalize cortisol levels in a mean time of 38 h. It has a good safety profile, with nausea, attributed to the rapid decrease in cortisol levels, occurring in two of the nine treatments.[13] Recently, administration of etomidate at low doses, as opposed to the high doses commonly used, has been shown to control hypercortisolism with no risk of occurrence of adrenal insufficiency, which would allow for use in standard hospitalization units.[14]

Two new contributions should be noted with regard to pasireotide. First, a clinical trial conducted with the short-acting formulation of pasireotide has been shown to significantly decrease tumor volume in patients with CD. This reduction was dose- and time-dependent: at 12 months, tumor volume reductions were achieved in 89% of patients treated with the 900 mcg dose given subcutaneously twice daily.[15] On the other hand, in another phase 3 trial, pasireotide long-acting formulation showed an improvement in clinical signs and health-related quality of life after 12 months of treatment. Such improvement occurred in some patients despite the lack of UFC control.[16]

CS diagnosis and management remains a challenge despite the most recent advances. To be sure, in the coming years we will have to be aware of new diagnostic approaches that allow for a better differential diagnosis with pseudo-CS and to improve the precision of etiological diagnosis of CS. The possibility of using new drugs, or others already known with new efficacy and safety data, as monotherapy or in combination will undoubtedly allow for improving the treatment of patients with CS, and it should not be forgotten that treating the comorbidities of these patients that so greatly impact their quality of life is equally important.

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