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EDITORIAL

An approach to screening for Cushing's syndrome in non-specialized health care settings

Una aproximación al cribado del síndrome de Cushing en un entorno asistencial no especializado

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Cushing's syndrome (CS) is caused by an excess of cortisol and/or glucocorticoids; if untreated, it results in a myriad of negative health outcomes contributing to increased morbidity and mortality.[1] Early diagnosis is of paramount importance to reduce this morbidity and mortality.

The diagnosis of CS is a considerable challenge even for experienced endocrinologists since there are no pathognomonic symptoms or signs of hypercortisolism. Most of the symptoms and signs of CS including obesity, hypertension, bone loss, and diabetes are common in the general population. These clinical features are found in individuals with metabolic syndrome; differentiating patients with metabolic syndrome from patients with CS might be a daunting task due to the current rapid increase of obesity rate in the general population. CS is considered a rare disease,[2] with an estimated incidence of 0.7–2.4 new cases per million people each year[3,4] and thus, routine screening for CS remains impractical. However, recent reports indicate that CS prevalence may be higher than previously thought in specific populations.[3] These include patients with hypertension, type 2 diabetes and osteoporosis (recently reviewed in[5]). According to the recent study, the prevalence of metabolic syndrome in Spain is 42% in men and 32% in women.[6] Although the criteria for metabolic syndrome slightly varies among different studies, similar values of metabolic syndrome prevalence in Spain have been reported in other works,[6] emphasizing the emerging prevalence of this condition in the general population. Considering the high prevalence of metabolic syndrome in Spain and the increased prevalence of CS in this at-risk population, a significant number of individuals with undiagnosed CS can be expected. Therefore there is an urgent need for the implementation of CS screening procedures, at least in specific populations.

The Endocrine Society guidelines recommend relying on clinical suspicion, and to screen for CS only in patients with highly suggestive signs and symptoms.[7] However, it is unclear which particular patients should be screened. Moreover, the suspicion of CS depends mainly on individual clinical judgment and experience, as patients might not always present with clear CS features.

We recently tried to develop a screening scoring system able to predict CS in specific, at-risk populations.[8] This model is based on the evaluation of clinical symptoms and signs and a single measure of an easy-to-use biochemical test, the late-night salivary cortisol test (LNSC). We decided to choose LNSC due to its good diagnostic sensitivity and specificity, and its non-invasive collection.[9] Also, our own group has determined it is a relatively high cost-effective technique.[10]

We performed a prospective multicenter study, CRISALIDA, *Cribado en Saliva de Alteraciones de Cortisol* (Screening for cortisol alterations with salivary samples) in 13 university hospitals in Spain under the auspices of the Spanish Society of Endocrinology and Nutrition. We screened a total of 353 at-risk patients with

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at least two of five non-specific features of CS: high blood pressure (defined as taking two or more drugs and having a systolic blood pressure over 140 mmHg and/or a diastolic blood pressure over 90 mmHg), obesity (body mass index >30), uncontrolled diabetes (HbA1c >7.0%), osteoporosis (T-score ≥ -2.5 SD), and virilization syndrome (hirsutism) with menstrual disorders. These clinical features were selected due to the previously described increased prevalence of CS in individuals with these conditions. In our population, the prevalence of CS was 7.4% (26 out of 353 patients) a value largely in line with studies performed in similar specific populations.[5,11]

To develop the diagnostic prediction model, we used signs and symptoms associated to CS which are relatively easy to document in regular clinical practice. Three clinical variables resulted positively and strongly associated with CS: muscular atrophy, dorsocervical fat and osteoporosis. The use of only these clinical variables was not sensitive and specific enough for screening CS. However, the addition of the LNSC test (with a cutoff level of 9.17 nmol/L) significantly improved the diagnostic ability of the model. Based on this predictive model, we generated a simple scoring system easy to use in clinical practice: muscular atrophy, 3 points; osteoporosis, 2 points; dorsocervical fat pad, 1 point; medium LNSC levels (between 9.17 and 13.93 nmol/L), 4 points; high LNSC levels (higher than 13.93 nmol/L), 5 points. These scores were based on the coefficients of the multivariate logistic regression model. Applying a cutoff score value of 4, the scoring system exhibited a sensitivity and specificity of 96.2% and 82.9%, respectively. Eighty three percent of the patients without CS were correctly identified while only 1 of 26 CS cases was missed. Our model yielded a sizable number of false positives, although perhaps acceptable for screening purposes. Most of the false positives obtained using our prediction model were due to their elevated LNSC levels without any signs and symptoms reminiscent of CS. A possible approach to further diminish the number of false positives (thus avoiding unnecessary tests) is that once all the potential CS are identified using our score model, positive patients with lower scores should be more carefully evaluated for the presence of clinical features before further evaluation for CS confirmation. Muscle atrophy might be particularly helpful in the CS screening process, since the proportion of false positive individuals with muscle atrophy was lower compared to the CS group.

While our results are encouraging, external validation of the model is absolutely required before considering wide implementation of the scoring system in non-endocrinological settings. We cannot formally rule out the possibility of selection bias in our study since the physicians undertaking the patients assessments were actually specialists and therefore, familiar with CS. In this regard, a blind prospective study comparing the use of our scoring system with, for example, clinical acumen might be particularly revealing.

In our study, all the assessments were performed by specialists and thus the conclusions only apply to this setting. We propose to test the scoring system in different non-endocrinological clinical settings such as primary care or hypertension clinics. Primary care would be a particularly interesting setting since it might significantly decrease the time to diagnosis of CS, something critical to avoid an excessive exposure to glucocorticoid excess and its consequent deleterious effects. We envision that if our model is to be developed for non-endocrinological specialists some background information should be added about how to properly evaluate and score these particular signs. On the other hand, the use of the LNSC test is not widely implemented in primary care context. However, LNSC has been shown to be a reliable diagnostic tool as indicated by the Endocrine Society's recommendation as a diagnostic tool. The easiness of use, inexpensiveness and noninvasiveness makes LNSC an optimal test for primary care clinics and other non-specialized health care settings.

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References

1. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015;386:913–27.
2. Steffensen C, Bak AM, Rubeck KZ, Jorgensen JO. Epidemiology of Cushing's syndrome. Neuroendocrinology. 2010;92 Suppl 1:1–5.
3. Tabarin A, Perez P. Pros and cons of screening for occult Cushing syndrome. Nat Rev Endocrinol. 2011;7:445–55.
4. Guaraldi F, Salvatori R. Cushing syndrome: maybe not so uncommon of an endocrine disease. J Am Board Fam Med. 2012;25:199–208.
5. Loriaux DL. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med. 2017;376:1451–9.
6. Marcuello C, Calle-Pascual AL, Fuentes M, Runkle I, Rubio MA, Montanez C, et al. Prevalence of the metabolic syndrome in Spain using regional cutoff points for waist circumference: the di@bet.es study. Acta Diabetol. 2013;50:615–23.
7. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93:1526–40.
8. Leon-Justel A, Madrazo-Atutxa A, Alvarez-Rios AI, Infantes-Fontan R, Garcia-Arnes JA, Lillo-Munoz JA, et al. A probabilistic model for Cushing's syndrome screening in at-risk populations: a prospective multicenter study. J Clin Endocrinol Metab. 2016;101:3747–54.
9. Elias PC, Martinez EZ, Barone BF, Mermejo LM, Castro M, Moreira AC. Late-night salivary cortisol has a better performance than urinary free cortisol in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 2014;99:2045–51.
10. Leon-Justel A, Mangas MA, Infante Fontan R, Castro Luque J, Venegas Moreno E, Madrazo Atutxa A, et al. Budget impact of using midnight salivary cortisol in the diagnosis of hypercortisolism. Clin Chim Acta. 2011;412:2248–53.
11. Catargi B, Rigalleau V, Poussin A, Ronci-Chaix N, Bex V, Vergnot V, et al. Occult Cushing's syndrome in type-2 diabetes. J Clin Endocrinol Metab. 2003;88:5808–13.