Human Corticotropin-Releasing Hormone tests: 10 years of real-life experience in pituitary and adrenal disease

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The $hCRH^{test}$ in patients with central adrenal insufficiency

In patients with central adrenal insufficiency (AI), a $hCRH^{test}$ could be used to distinguish hypothalamic from pituitary disease[1], or to suggest a very early phase of Addison's disease in patients with autoantibodies[2]. A good diagnostic accuracy has been reported in patients with hypopituitarism[3], but its sensitivity is lower than that of the insulin tolerance test[4]. The role of $hCRH^{test}$ in AI is consequently still a matter of debate[5,6].

Central AI was suspected in patients with known pituitary-hypothalamic disease (neoplastic lesion, brain surgery or radiotherapy, traumatic or vascular brain injury, or after glucocorticoid withdrawal), and signs or symptoms of AI (hyponatremia, fatigue, hypoglycemia). AI was diagnosed if basal morning serum cortisol was <83 nmol/L, or peak ACTH in the low-dose short synacthen test (LDSST, 1μg) was <500 nmol/L[5].

Patients with suspected AI (n=25) had lower $basal^{cortisol}$ levels than those with pseudo-CS or CD (Table 1). At the end of the diagnostic work-up, AI was ruled out in 14/25 (56%) patients; a pituitary and a hypothalamic origin was confirmed in 5 and 6 patients, respectively. Considering a follow-up of at least 12 months, all patients without AI did not show signs or symptoms of acute adrenal crisis, and glucocorticoid replacement treatment was not introduced.

$Basal^{cortisol}$ levels and $AUC^{cortisol}$ after $hCRH^{test}$ were lower in patients with AI than in those with an adequate HPA axis function (as reported in Supplementary table 1). $Basal^{cortisol}$ >215 nmol/L and $AUC^{cortisol}$ >44767 proved sufficiently accurate in ruling out AI (with a SE 85.7%, SP 72.7%, AUC 0.844, and a SE 85.7%, SP 63.6%, AUC 0.734, respectively).

Basal and hCRH-stimulated ACTH and cortisol levels were of no further help in diagnosing AI, and their levels were similar in patients with a hypothalamic as opposed to a pituitary etiology of AI (as summarized in

Supplementary figure 2). Considering ACTH or cortisol levels after hCRH injection, the curve of patients with AI of pituitary origin had a different profile (more reduced and blunted) from those with AI of hypothalamic origin. Further studies on larger populations are needed to ascertain whether $hCRH^{test}$ can differentiate central AI.

An accurate diagnosis of central AI is essential in patients with hypothalamic or pituitary injury. Corticotropin testing can detect only a reduced adrenal response to ACTH[1]. The insulin tolerance test is unable to distinguish central AI because CRH only stimulates the secretion of ACTH at pituitary level. While the role of the $hCRH^{test}$ in patients with suspected hypercortisolism is well established, its diagnostic accuracy in AI, or in differentiating hypothalamic from pituitary HPA axis impairment, is still debated[7]. In our study, we did not perform $hCRH^{test}$ in controls, and we can only consider subjects without AI as adrenal sufficient. Basal cortisol levels and hCRH-stimulated $AUC^{cortisol}$ could suggest AI (both SE >80%), but their role in excluding subjects with a normal HPA axis was limited (SP ≈70%), as previously reported[4].

In our series, the $hCRH^{test}$ was unable to differentiate between a hypothalamic and a pituitary origin of AI, for which clinical judgment, corticotropin testing and expertise are mandatory[8].

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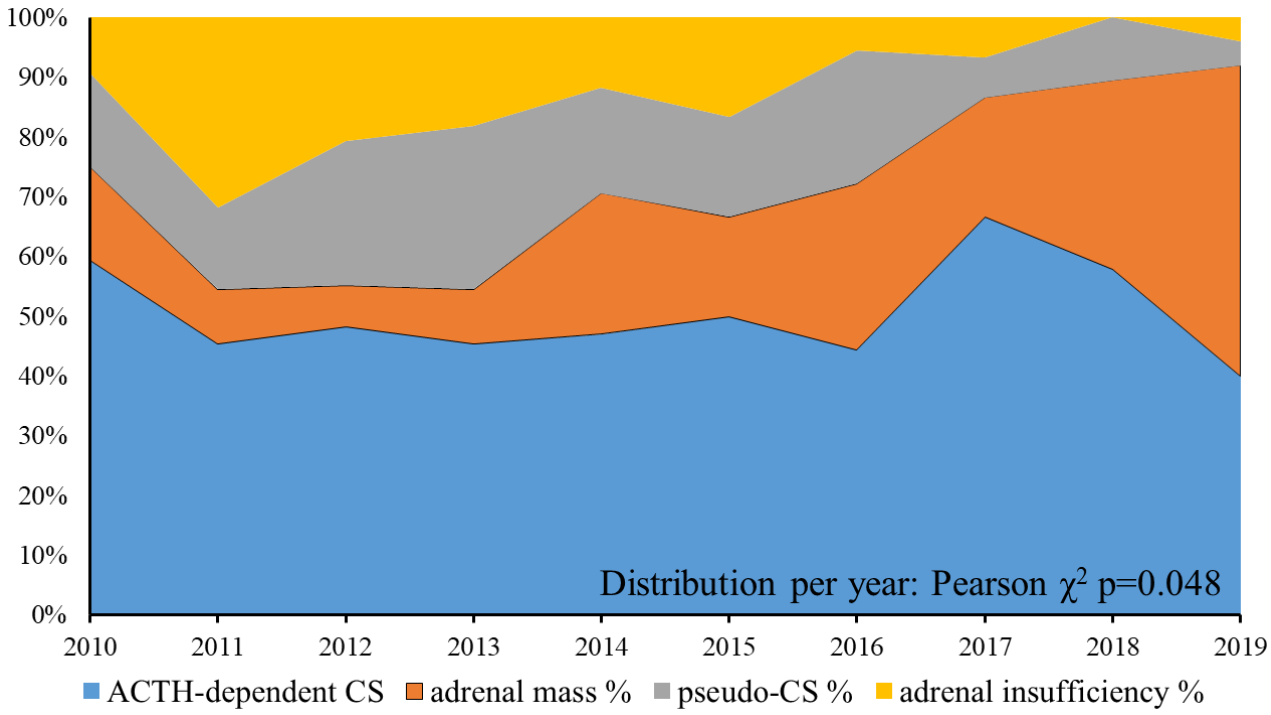
Supplementary table 1: Patients' basal and post-hCRH characteristics. Adrenal sufficiency: patients with a normal hypothalamic pituitary adrenal axis. AI: adrenal insufficiency; AUC: area under the curve. a: $p<0.05$ vs adrenal sufficiency.

	Adrenal sufficiency n=14	**AI n=11**	**Pituitary AI n=5**	**Hypothalamic AI n=6**
ACTH morning (pg/mL)	21.5 (4.2)	13.7 (2.3)	15 (3.9)	12 (2)
$Basal^{ACTH}$ (pg/mL) $hCRH^{test}$	30.1 (9.5)	12 (1.8)	11.8 (2.4)	13.2 (3.2)
$Basal^{cortisol}$ (nmol/L) $hCRH^{test}$	311 (31.6)	160 (30.4) [a]	147.5 (62.2)	155.2 (28.1)
$Peak^{ACTH}$ (pg/mL) $hCRH^{test}$	85.2 (27.4)	48 (10.2)	36.2 (12.9)	65.8 (15.7)
$Peak^{cortisol}$ (nmol/L) $hCRH^{test}$	530.7 (69.4)	343 (66.3)	277 (136.2)	402.4 (60)
$\Delta\%^{ACTH}$	2.14 (0.46)	3.4 (0.97)	2.31 (1.25)	4.76 (1.61)
$\Delta\%^{cortisol}$	0.84 (0.2)	1.1 (0.31)	0.52 (0.28)	1.8 (0.47)
AUC^{ACTH}	6371 (1577)	3861 (687)	3171 (855)	4983 (1094)
$AUC^{cortisol}$	54855 (5110)	36052 (6672) [a]	29563 (13891)	41658 (5745)

Supplementary Figure 1: Indication of hCRH^{test} over the years from 2010 to 2019.



Supplementary figure 2: ACTH and cortisol curve during hCRH^{test} in patients with normal adrenal function, adrenal insufficiency (AI), pituitary AI and hypothalamic AI.