Prolactine and urinary free cortisol measurement improve inferior petrosal sinus sampling results in ACTH dependent Cushing´s Syndrome

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Introduction: ACTH-dependent Cushing´s syndrome (CS) is usually caused by a pituitary corticotroph adenoma (Cushing's disease).
Inferior petrosal sinus sampling (IPSS) is considered to be the gold standard for confirming the source of ACTH secretion in patients with CS. Prolactin measurement during IPSS can improve diagnostic accuracy, reduce false negative response and can also clarify those cases considered as non-typical responses.

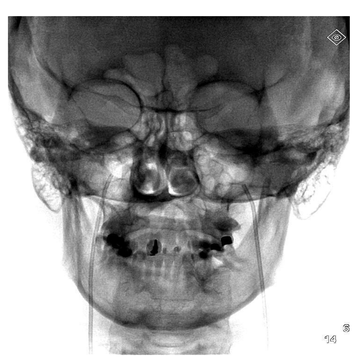


FIGURE 1: Catheters in petrosal sinus

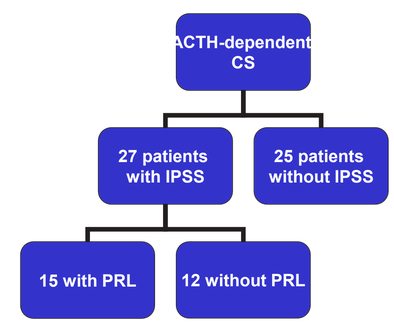
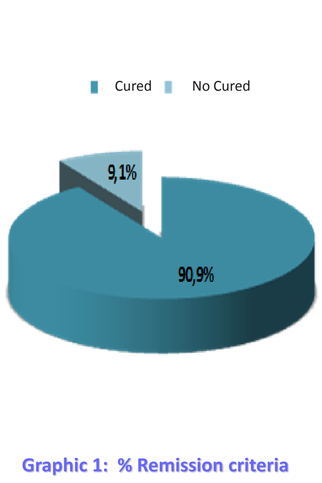
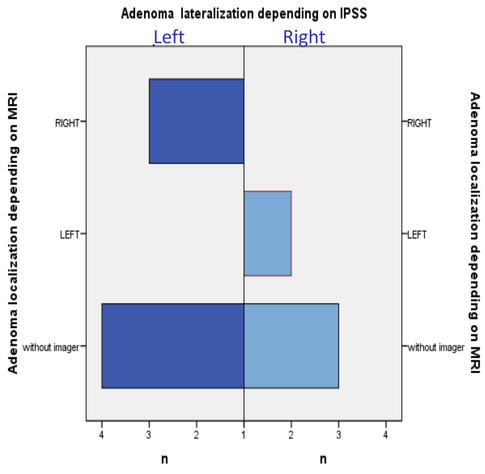


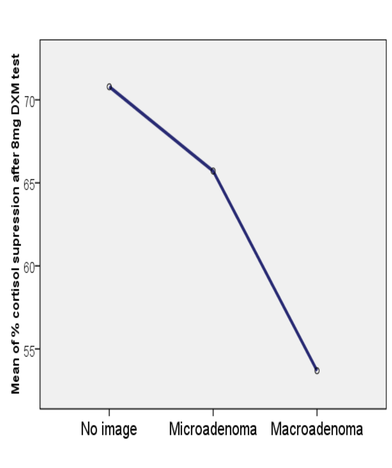
FIGURE 2: ACTH-dependent Cushing Syndrome (CS)



Graphic 1: % Remission criteria



Graphic 2: Discordances between MRI and IPSS lateralization



Graphic 3: Mean of DXM 8 mg supression depending on MRI result

Patients and methods: 56 patients with ACTH-dependent CS were included (45 F/11 M, mean age 43'6±10'8 years and 90,1 % Cushing´s disease) diagnosed since 2000. Localization test were analyzed; DXM 8 mg test, pituitary MRI and IPSS with and without PRL measurement.
IPSS was performed in 27 cases (15 with PRL measurement, 2 excluded due to incomplete data). Depending on IPSS results were classified as typical IPSS response if basal ACTH ratio Central/peripheral (C/P) was > 2 and/or after CRH> 3, considering others as atypical. Response to surgical treatment and utility of PRL determination were analyzed.

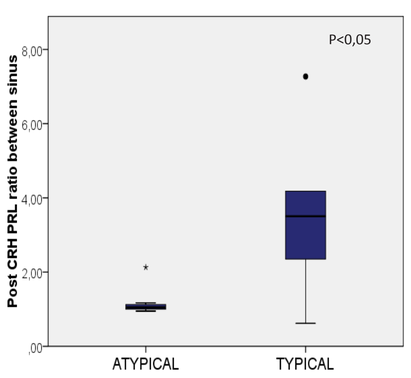
$$\frac{\text{Dominant peak post-CRH IPS ACTH/Peripheral post-CRH ACTH}}{\text{Ipsilateral basal IPS PRL/Peripheral basal PRL}} = \text{Normalized ACTH/PRL IPS:P ratio}$$

FIGURE 3: Normaliced ACTH/PRL IPSS:P ratio (PRL correction) [2]

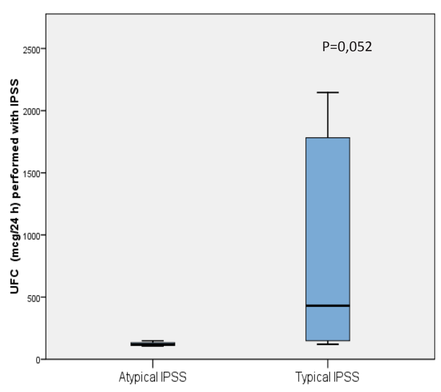
	Peak minute	Basal ACTH C/P ratio	Post CRH Ratio ACTH C/P	Post CRH PRL ratio between sinus	Basal PRL Ratio C/P	Basal PRL between sinus	PRL correction (Findling 2004)
Atypical N=7	16'25 ±10'31	1'07 ±0'12	1'78 ± 0'33	1'2 ± 0'46	1'04 ± 0'27	1'14 ± 0'16	1'76 ± 0'54
Typical N=6	3 ± 1'78	4'36 ± 2'94	25'77 ± 13'01	3'57 ± 2'2	1'87 ± 1'15	2'3 ± 1'9	17'55 ± 10'95
p	**0'017**	**0'028**	**0'004**	**0'054**	0'078	0'173	**0'004**

Table 1: Differences between typical and atypical IPPS .

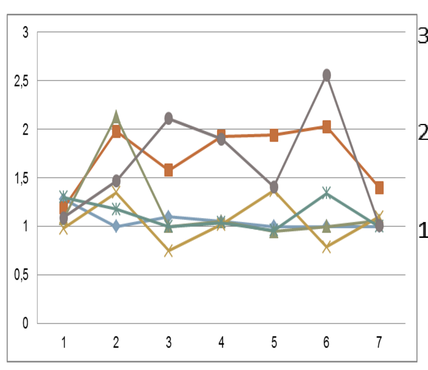
Results: ACTH-dependent CS was classified as Cushing´s disease in 90,9 % and ectopic tumor in 9,1 %. Remission criteria was achieved in 90,9 % (100 % microadenomas) confirmed by surgical identification and postoperative adrenal insufficiency, with posterior recurrence in 21,4 % in the following 21±14,15 months. Toraco-abdominal CT was performed in 45 % patients and incidental suprarrenal image was found in 25 % patients.
Cortisol response to high DXM suppression test was > 50% in 62'9%, and > 90% in 37% in Cushing´s disease. Preoperative pituitary MRI did not identify adenoma in 12.5%. MRI adenoma lateralization was concordant with surgical adenoma lateralization in 92,7 %. IPPS was typical in 46,3% (6/13) and there were significant differences between typical vs atypical (basal ACTH C/P ratio, post CRH ACTH C/P ratio, peak time, post CRH PRL ratio between sinus, and PRL correction).
Urinary free cortisol (UFC) perfomed with IPSS was significantly higher in typical IPPS (843'12±890 vs 123'6±22'7 mcg/24 h, p= 0'052) and also UFC values >3 NRV (p=0'040). Four patients with atypical IPPS corrected with PRL were surgically treated and they meet remission criteria up to today.
After transsphenoidal surgery 90.9% of patients met remission criteria (100% of microadenomas and in those without previous MRI image).



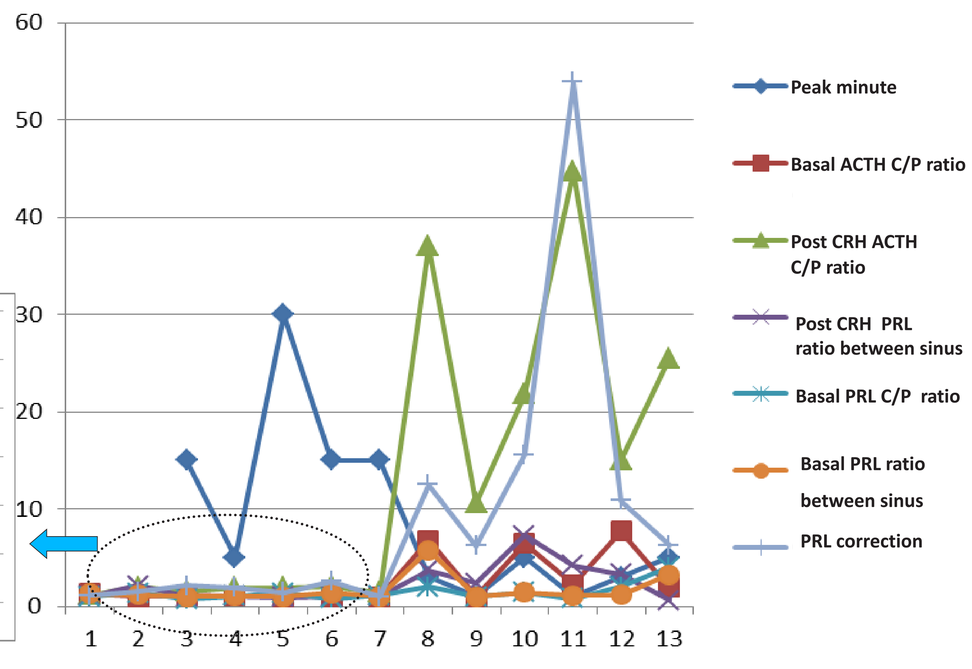
Graphic 4: PRL ratio between sinus at peak response depending on IPSS (atypical vs typical)



Graphic 5: UFC mean depending on IPPS (atypical vs typical)



Graphic 6: Atypical IPSS ratios (extended)



Graphic 7: Calculated IPSS ratios

Discussion: Basal PRL ratio C/P was <1.8 in all atypical IPPS and 50% of typical IPPS. Venograms were reviewed and ACTH C/P peak corrected with PRL was> 0.8 in Cushing´s disease, being most of them > 1.2 (5/7). Only two patients have an intermediate value (a cyclic Cushing´s disease 1,09 and a microadenoma 1,05) [1,2]. PRL values calculated after CRH showed differences between typical IPSS and atypical IPPS patients p=0'054)[1]. This elevation of PRL after CRH and its use in ratio correction doesn´t interfere with ACTH C/P peak.

Conclusions: **PRL measurement in atypical IPSS allows reclassification, whereas in typical cases can be useful to validate the peak ACTH C/P. PRL elevation after CRH and its use in the correction of the ACTH C/P ratio does not interfere with the interpretation of ACTH C/P peak. It is essential to evaluate UFC to complete the assessment.**

Bibliography
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