

Is there a suitable front-line test for discriminating hypopituitarism in patients with an isolated low free T4 detected on routine thyroid screening?

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Introduction

- Hypopituitarism is a rare disorder associated with low free T4 (FT4) and normal TSH levels.
- Assay imprecision and reagent lot-to-lot variability (Beckman Coulter UniCel DXI 800) can have a significant impact on the number of low FT4 results produced by a high-throughput laboratory.
- This can lead to an increase in follow-up testing and Endocrine referrals to exclude pituitary pathology.
- The aim of this project was to identify a suitable add-on test which could help to rule out hypopituitarism in low-risk patients with isolated low FT4.

Methods

- 49 patients (12 female, 37 male) with known pituitary adenoma who had a low FT4 result at diagnosis were used to calculate the sensitivity of LH, FSH, testosterone and cortisol at a variety of cut-off values.
- 50 GP patients (42 female, 8 male) with isolated low FT4 in whom pituitary disease was excluded by Endocrine review or MRI scan were used to calculate the specificity.

Results and discussion

- 1388 GP patients had isolated low FT4 between January 2019 and July 2020. 142 (10.2%) had follow-up pituitary hormone tests, of which 59 (4.3%) were referred to secondary care for further investigation.
- Table 1 shows the cut-off value for each analyte that yielded >97% sensitivity for detecting hypopituitarism.
- LH \leq 4 IU/L was the most sensitive and specific test for detecting pituitary disease in females.
- Total testosterone \leq 8 nmol/L was the best performing test in males but this study was based on early morning samples. LH \leq 4 IU/L would be the more applicable test for the random samples received for thyroid screening.
- Positive and negative predictive values for LH \leq 4 IU/L in males and females are shown in table 2.
- Four of the 59 GP patients who were referred to secondary care were diagnosed with pituitary pathology; all of these had an LH \leq 4 IU/L. Only one of the 49 patients in the adenoma cohort had an LH >4 IU/L.
- Larger patient cohort sizes are required for increased confidence in the calculated sensitivity and specificity.

Table 1. Sensitivity and specificity of different hormones and cut-offs

Hormone (sex) and cut-off	Sensitivity (95% CI)	Specificity (95% CI)
LH (F) \leq 4.0 IU/L	100% (73.5, 100.0)	78.1% (62.4, 89.4)
FSH (F) \leq 64.0 IU/L	100% (73.5, 100.0)	19.5% (8.8, 34.9)
LH (M) \leq 4.0 IU/L	97.1% (85.1, 99.9)	50.0% (15.7, 84.3)
FSH (M) \leq 32.0 IU/L	97.2% (85.5, 99.9)	0.0% (0.0, 36.9)
Testosterone (M) \leq 8 nmol/L	97.2% (85.5, 99.9)	87.5% (47.4, 99.7)
Cortisol (M/F) <500 nmol/L	100% (92.1, 100.0)	0.0% (0.0, 7.1)

Table 2. Positive and negative predictive values for LH with a cut-off of \leq 4 IU/L in males and females.

	Positive predictive value*	Negative predictive value*
LH \leq 4 IU/L in females	1.30%	100%
LH \leq 4 IU/L in males	0.57%	100%

* Based on an estimated disease prevalence of 0.29%

Conclusions

- LH >4 IU/L is the most appropriate test for ruling out pituitary disease in low-risk patients with isolated low FT4.
- LH could be added reflectively to samples with isolated low FT4 to exclude the possibility of pituitary pathology.
- If LH \leq 4 IU/L then follow up with a full pituitary hormone profile would be advised.

