Question 82
A 25-year-old woman with no significant past medical history presents with weight gain, depression, easy bruising and proximal muscle weakness. On examination she has a plethoric complexion, central obesity with striae and a proximal myopathy. Investigations reveal low plasma concentrations of cortisol and adrenocorticotrophic hormone (ACTH). Which of the following is the most likely diagnosis?
A. Cushing's disease.
B. Pseudo-Cushing's syndrome.
C. Factitious Cushing's syndrome.
D. Ectopic ACTH syndrome.
E. Cortisol-producing adrenal adenoma

Cushing syndrome
i. result directly from chronic exposure to excess glucocorticoid
ii. this patient has Cushing's syndrome with her clinical presentation

ACTH Dependent Cushing's Syndrome

- Pituitary adenoma
- Usually microadenomas, 5% macroadenomas
- Macroadenomas are more likely to have high plasma ACTH concentrations compared to those of macroadenomas.
- Increased cortisol secretion:
  i. increased urinary excretion of cortisol and 17-OHCS
  ii. inhibits hypothalamic CRH secretion
  iii. inhibits ACTH secretion by normal nonadenomatous pituitary corticotrophs- atrophy
  iv. concentration of CRH in cerebrospinal fluid are reduced

Ectopic ACTH syndrome
- Nonpituitary tumour secretion of ACTH – usually carcinomas (lung, pancreas, thymus)
  i. Small-cell carcinoma of lung – arise from neuroendocrine cells in the distal bronchioles
  ii. ACTH secreting pancreatic and thymic tumours are carcinoid tumors arising from neuroendocrine cells
- Tumor ACTH secretion is not inhibited by cortisol or other glucocorticoids

Ectopic CRH syndrome
CRH secretion by tumor causes hyperplasia and hypersecretion of pituitary corticotrophs
ACTH hyperssecretion, cortisol hypersecretion & bilateral adrenal hyperplasia
Many of these tumours also secrete ACTH- in inhibited by dexamethasone

ACTH-Independent Cushing's Syndrome
Primary adrenocortical hyperfunction

- Increased cortisol secretion suppresses both CRH and ACTH secretion
- Normal pituitary corticotrophs, normal zonae fasciculata and reticularis of adrenal glands atrophy
- Serum dehydroepiandrosterone (DHEA-S) concentrations and urinary excretion of DHEA-S and 17 KS are low relative to urinary 17-OHCS or cortisol excretion

Bilateral micronodular hyperplasia

- Sporadic and familial forms
- Carney's complex: familial form
- Autosomal dominant
- 2 major types of findings:
  i. pigmented lentigines
  ii. blue nevi on face, neck, and trunk, including the lips, conjunctivae, sclerae
  iii. multiple neoplasms – endocrine (testicular Sertoli cells and occasionally adrenal, pituitary or thyroid) and non endocrine (cutaneous, mammary, atrial myxomas)

Bilateral ACTH-independent macronodular hyperplasia

- Associated with adrenal glands that weigh from 24-500g
- Contain multiple nonpigmented nodules greater than 5 mm in diameter
- Nodules appear to be typical benign adrenal nodules
- Pathology
  i. Overexpression of eutopic receptors
  ii. Inappropriate expression of ectopic receptors
  iii. Coupling of eutopic receptors to steroidogenic signalling pathways

Factitious Cushing's syndrome

- Rare, < 1% of pts
- Refers to surreptitious intake of glucocorticoid
- Difficult to detect from history and difficult to exclude with laboratory tests
- Dx:
  i. low or erratic values for urinary cortisol - suggestion of of ingestion of a synthetic glucocorticoid or intermitten ingestion of cortisol or cortisone
  ii. Excessive urinary cortisol relative to serum cortisol concentrations – suggestion of addition of hydrocortisone to urine specimens
  iii. Detection of synthetic glucocorticoids in urine

Pseudo-Cushing's syndrome

Hypercortisolism:

- Physically stressed
- Severe obesity – visceral obesity, polycystic ovary syndrome
- Psychological stress- severe major depressive disorder or melancholic syndrome (refer to Tricia's question 2003 P1 Q 16)
- Chronic alcoholism

Back to the question:

Patient does have symptoms of Cushing's syndrome. The question is whether the blood test show a ACTH dependent or independent syndrome. Her cortisol level and ACTH are low

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cortisol</th>
<th>ACTH</th>
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<tbody>
<tr>
<td>Cushings disease</td>
<td>increased</td>
<td>suppressed</td>
</tr>
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Answer is C Factitious Cushing's syndrome
Diagnostic test

24hr urinary cortisol excretion
basal urinary cortisol excretion is more that 3X the upper limit of normal – diagnostic of Cushing’s syndrome

up to 40% of patients with severe depression or polycystic ovary syndrome may have slightly high 24hr urinary cortisol excretion
people who drink very large volumes of liquid also excrete more cortisol while excretion of Cr and 17 hydroxycorticosteroids remain unaltered.
If more than 3L of urine volumes- urinary cortisol excretion should be interpreted with caution

Low dose dexamethasone suppression test
Exogenous dexamethasone substitutes for endogenous cortisol in suppressing ACTH release

Low dose dexamethasone:
To differentiate patients with Cushing’s syndrome of any cause from patients who do not have Cushing’s syndrome.
Dexamethasone dose (1mg)

High dose dexamethasone:
To differentiate patients with Cushing’s disease from patients with ectopic ACTH syndrome