gained considerable experience\textsuperscript{5}. Although BIPSS is well tolerated, very occasional side effects have been reported including brainstem vascular damage and haematomas.\textsuperscript{87–89} Cavernous sinus sampling (CVS) is also a powerful method for differentiating CD from EAS, although tumour localization by CVS can not accurately predict the adenoma site at surgery and therefore it should not be used to guide surgical resection.\textsuperscript{90}

Differentiating CD from pseudo-Cushing’s states

A pseudo-Cushing’s state comprises some clinical features of CS together with evidence of hypercortisolism, which however resolves following resolution of the primary state, such as the depressed phase of affective disorders,\textsuperscript{91} alcoholism or withdrawal from ethanol intoxication\textsuperscript{92,93} as well as eating disorders (anorexia and bulimia nervosa)\textsuperscript{91} (Table 4). The differentiation between mild CS and pseudo-Cushing’s state is often difficult, as laboratory investigations characteristic of CS, such as elevated UFC, disruption of the normal diurnal cortisol secretion, and lack of plasma cortisol suppression to the DST, may be encountered in both conditions. Definitive biochemical confirmation may be difficult and require repeated testing, although the history may be suggestive and clinical and physical examination may indicate the correct diagnosis of either CS or pseudo-Cushing’s state. The hypercortisolism associated with these states is probably centrally mediated through increased secretion of CRH and activation of the HPA-axis, in contrast to the great majority of patients with CS who have suppressed hypothalamic CRH secretion.\textsuperscript{53}

A direct comparison of commonly used diagnostic tests between patients with CS and pseudo-Cushing’s states showed that a post LDDST serum cortisol value of 38nmol/l or more was associated with a sensitivity and a specificity of 90\% and 100\%, respectively, for diagnosing CS.\textsuperscript{1} Patients with CD also demonstrated a more pronounced ACTH and/or cortisol response to CRH than patients with pseudo-Cushing’s states.\textsuperscript{91–93} Administration of CRH in depressed patients is associated with blunted ACTH and cortisol responses, although there is considerable overlap with CD; similarly, administration of DDAVP was associated with a high specificity but relatively low sensitivity.\textsuperscript{55,91} Depressed patients usually demonstrate adequate cortisol response to insulin induced hypoglycaemia (blood glucose levels less than 40mg/dl, 2.2mmol/l), which is also absent in approximately 10\% of patients with CS.\textsuperscript{34,35} In an effort to further improve the diagnostic accuracy, CRH administration following a formal 48 hour LDDST has been used; a post 15min CRH administration serum cortisol value greater than 38nmol/l (1.4μg/dl) was found in all patients with CS but none with a pseudo-Cushing’s state, thus providing a sensitivity and a specificity of 100\%.\textsuperscript{44} Serum cortisol response following the administration of the opiate antagonists loperamide and naloxone has also been used, but this test has not adequately been validated.\textsuperscript{13} In distinguishing alcohol induced pseudo-Cushing’s from CS, the clinical history and blood alcohol level, when detectable, may be of great value.\textsuperscript{1,13} Measurement of serum midnight cortisol may be another means of differentiating pseudo-Cushing’s states from CS; however, the diagnostic accuracy of this investigation requires hospital admission and has not been tested in a large number of patients with documented pseudo-Cushing’s states.\textsuperscript{1,38} More recently it has been suggested that measurement of salivary midnight cortisol may be as accurate as serum midnight cortisol in distinguishing CS from severe obesity and can be used as an alternative tool.\textsuperscript{39} A rare condition that can potentially cause further diagnostic confusion is generalized glucocorticoid resistance state, due to mutations in the ligand binding domain of the glucocorticoid receptor.\textsuperscript{94–96} Such patients have high ACTH and cortisol levels and resistance to dexamethasone suppression, since there is diminished feedback by glucocorticoids; however, they exhibit preservation of the normal circadian rhythm of cortisol secretion although set at a higher level.\textsuperscript{1}

Table 4. Pseudo-Cushing’s and ‘Cushingoid’ like states

<table>
<thead>
<tr>
<th>Pseudo-Cushing’s states</th>
<th>‘Cushingoid’ like states</th>
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<tbody>
<tr>
<td>Alcoholic pseudo-Cushing’s syndrome</td>
<td>Obesity</td>
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<tr>
<td>Depression</td>
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<td>Eating disorders</td>
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