Cushing's Syndrome and Treatment-Resistant Depression

Sir,
Anil Kumar and Grover[1] report a case of Cushing's syndrome which presented as treatment-resistant depression. This report is instructive for diagnosis and management of Cushing's syndrome in treatment-resistant depression.

First, although, the title suggests that patient had "Cushing's syndrome," the report does not mention any clinical or biochemical abnormalities suggestive of Cushing's syndrome except depression. Nonpsychiatric symptoms of Cushing's syndrome include central obesity, facial plethora, round face, purple striae, easy bruising of the skin, and muscle weakness. These symptoms are accompanied by clinical and biochemical signs of treatment-resistant hypertension, hyperglycemia, osteoporosis, hypokalemia, and nephrolithiasis.[2] Thus, the diagnosis of Cushing's syndrome, in this case, rests solely on laboratory evidence of hypercortisolemia. Authors have reported raised plasma cortisol (722.7 nmol/L, laboratory reference: 193–634 nmol/L).[1] Plasma cortisol has a well-defined circadian rhythm. Thus, it is important to mention the time at which sample was collected. Further, cortisol secretion increases during periods of stress like hospitalization and electro-convulsive therapy. For this reason, it is suggested that 24-h urinary free cortisol or midnight plasma cortisol should be used as a screening test for Cushing's syndrome.[2] Authors also report dexamethasone nonsuppression, which is a frequently used test to diagnose Cushing's syndrome. The case report does not mention the protocol of dexamethasone suppression test used in this case. Importantly, nonsuppression of cortisol levels with low-dose dexamethasone (1 mg) is expected in patients suffering from severe depression.[3] In such cases, a slightly cumbersome test which involves administration of 0.5 mg of dexamethasone at intervals of 6 h for 2 days and collection of two plasma samples is more appropriate.[2] Keeping in mind, that this patient also had an adrenal mass suggestive of adrenal adenoma, it falls in a difficult to diagnose category called subclinical Cushing's syndrome with an "Incidentaloma."[4]

Second, authors report complete remission of depression with a combination of venlafaxine 300 mg/day and ketoconazole 400 mg/day.[1] There are important pharmacokinetic considerations involved in this combination. Venlafaxine is extensively metabolized to an active metabolite, desvenlafaxine mediated by cytochrome *P* 2D6 (CYP2D6). Venlafaxine and desvenlafaxine undergo transformation to inactive metabolites mediated by CYP3A4, CYP2C19, and CYP2C9.[5] Ketoconazole is a strong CYP 3A4 inhibitor. Thus, a clinically significant interaction between Venlafaxine and Ketoconazole is likely. The magnitude of this interaction depends on CYP2D6 activity. CYP2D6 activity depends on multiple genetic polymorphisms. Lindh *et al.* have reported that venlafaxine exposure is doubled when administered with ketoconazole in subjects who are CYP2D6 poor metabolizers.[6] At present, we do not have extensive data about CYP2D6 polymorphism in the Indian population, and poor metabolizers are reported at <1% frequency.[7] Nevertheless, clinicians need to consider this possibility. A patient who has low CYP2D6 activity and receives venlafaxine and ketoconazole will be exposed to toxic concentrations of Venlafaxine. This can present as a sympathomimetic syndrome, cardiovascular instability, and life-threatening cardiac arrhythmias.[8]

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