The differential diagnosis for Cushing's disease (caused by an ACTH-secreting pituitary adenoma) involves distinguishing it from other causes of Cushing's syndrome, which includes a variety of conditions leading to excess cortisol. The differential diagnosis includes:

1. Cushing's syndrome (exogenous and endogenous) Exogenous Cushing's syndrome: Usually caused by chronic use of glucocorticoid medications. Endogenous Cushing's syndrome: Includes both ACTH-dependent and ACTH-independent causes. 2. ACTH-Dependent Causes: Cushing's disease: ACTH-producing pituitary adenoma (most common endogenous cause). Ectopic ACTH secretion: Tumors outside the pituitary (e.g., small-cell lung carcinoma, bronchial carcinoids) can produce ACTH, leading to cortisol excess. Ectopic CRH secretion: Rare tumors that secrete corticotropin-releasing hormone (CRH), which stimulates ACTH production by the pituitary. 3. ACTH-Independent Causes: Adrenal adenoma or carcinoma: Autonomous cortisol production from an adrenal mass without ACTH stimulation. Adrenal hyperplasia: Bilateral adrenal hyperplasia can cause excessive cortisol production. Primary pigmented nodular adrenal disease (PPNAD): A rare cause in younger patients, often associated with Carney complex. 4. Pseudo-Cushing’s syndrome: Conditions that mimic Cushing's syndrome due to increased cortisol but resolve when the underlying issue is treated. Common causes include: Chronic alcoholism Severe depression Obesity Poorly controlled diabetes mellitus 5. Polycystic Ovary Syndrome (PCOS): PCOS shares features like hirsutism, obesity, and menstrual irregularities with Cushing’s, though it does not involve cortisol excess. Diagnostic tools for differentiation include: 24-hour urinary free cortisol: To assess cortisol overproduction. Low-dose dexamethasone suppression test: To differentiate between Cushing’s syndrome and pseudo-Cushing’s. ACTH levels: Low in adrenal causes, high in pituitary or ectopic ACTH production. High-dose dexamethasone suppression test: Suppression of cortisol in Cushing's disease (pituitary source), but not in ectopic ACTH syndrome. Imaging: MRI for pituitary tumors, CT or MRI for adrenal tumors or ectopic ACTH sources. By combining clinical presentation, biochemical testing, and imaging, these conditions can be differentiated from Cushing's disease.

They should not be confused with ectopic Cushing syndrome or exogenous steroid use.

see Ectopic corticotroph adenoma.

see Silent corticotroph adenoma.

Ectopic ACTH/CRH co-secreting tumors are extremely rare in children and adolescents. The diagnosis of this condition is frequently missed and is sometimes confused with CD due to the effect of CRH on the pituitary [1)]

1)
Karageorgiadis AS, Papadakis GZ, Biro J, Keil MF, Lyssikatos C, Quezado MM, Merino M, Schrump DS, Kebebew E, Patronas NJ, Hunter MK, Alwazeer MR, Karaviti LP, Balazs AE, Lodish MB, Stratakis CA. Ectopic adrenocorticotropic hormone and corticotropin-releasing hormone co-secreting tumors in children and adolescents causing cushing syndrome: a diagnostic dilemma and how to solve it. J Clin Endocrinol Metab. 2015 Jan;100(1):141-8. doi: 10.1210/jc.2014-2945. PubMed PMID: 25291050.