Diagnosis and Clinical Genetics of Cushing Syndrome in Pediatrics

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KEYWORDS

• Pituitary gland • Adrenal gland • Cyclic AMP (cAMP) • *PRKAR1A* gene • *AIP* gene • *ARMC5* gene • *USP8* gene • *GNAS1* gene

KEY POINTS

- Cushing syndrome (CS) in pediatrics is rare, and unless recognized early, it can lead to significant morbidity and even mortality.
- Pituitary adenomas (Cushing disease) are treated best by complete excision; successful transsphenoidal surgery remains the cornerstone of therapy and the sole determinant of long-term cure.
- Bilateral adrenocortical hypeprlasias are new causes of corticotropin-independent CS; they can be difficult to diagnose owing to their rarity and often insidious or cyclical clinical presentation.
- Adrenocortical cancer is a rare cause of CS, but should be excluded in any patient with corticotropin-independent CS, especially among younger patients.
- Pituitary adenomas and adrenocortical tumors are often caused by germline or somatic mutations in a list of genes with implications for patients and their families.

INTRODUCTION: EPIDEMIOLOGY OF CUSHING SYNDROME AND CLINICAL PRESENTATION

Endogenous Cushing syndrome (CS) is a rare entity, especially in children.[1,2] The overall incidence of CS is approximately 2 to 5 new cases per million people per year; of these cases, only approximately 10% each year occur in children.[1] As in adult patients, in children and adolescents with CS there is an overall female-to-male predominance, which decreases with younger age; there might even be a male-to-female predominance in infants and young toddlers.[3]

Like the exogenous forms, endogenous CS is owing to chronic exposure to excess glucocorticoids. All patients with CS have a classic presentation (**Fig. 1**): facial

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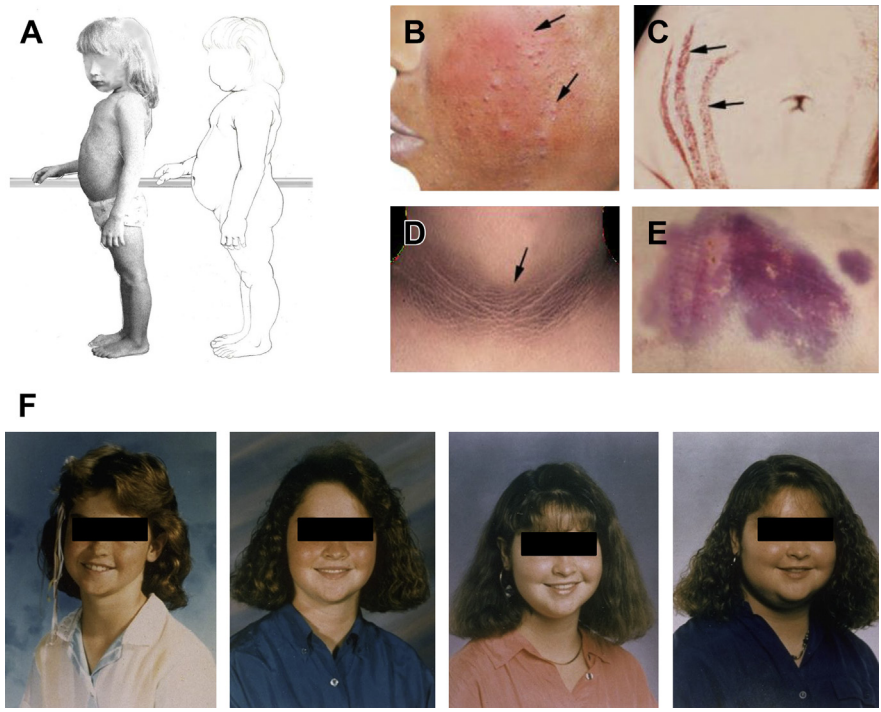

Fig. 1. (*A*) Progression from a normal somatotype to that of Cushing syndrome in a young child: unlike in older children and adults, thinning of the extremities is not as obvious; however, accumulation of abdominal fat and rounding of the face are obvious. (*B*) Facial plethora with acne (*arrows*) in a patient with Cushing syndrome. (*C*) Striae with bleeding (*arrows*). (*D*) Acanthosis nigricans (*arrows*) in a patient with Cushing syndrome and severe insulin resistance and glucose intolerance. (*E*) Skin bruising is frequent in older patients with Cushing syndrome, but absent in toddlers and young children. (*F*) The gradual facial changes of a pediatric patient with Cushing syndrome over 4 years.

plethora,[4] central body weight gain with limb thinning, glucose intolerance or diabetes[5] with extensive acanthosis nigricans, hypertension, osteoporosis and fractures,[6] proximal muscle weakness, opportunistic infections (including fungal infections of the skin), easy bruising, and striae.[7] However, by the time this presentation is fully developed, cure of the syndrome, especially of pituitary tumors, is less likely and comes with significant postoperative morbidity. Thus, the goal of the clinician should be to diagnose CS early (see **Fig. 1**F), well before the classic stigmata of CS (see **Fig. 1**) have developed. This is very important because even in individuals with hereditary types of CS, there is variable penetrance: although most patients present with severe CS, cyclical or atypical CS may be insidious. It should be noted that morbidity and mortality are increased in CS, with a standard mortality ratio between 2 and 4.[2]

The clue to early diagnosis of CS in children is delayed growth that occurs simultaneously with increasing weight gain.[8] This is obvious in the growth chart of the patients that are still growing (**Fig. 2**), well before full clinical symptoms develop.

CAUSES OF ENDOGENOUS CUSHING SYNDROME IN CHILDREN AND ADOLESCENTS

The most common cause of endogenous CS in children is corticotropin (ACTH) overproduction from the pituitary; this is called Cushing disease (CD).[1] It is usually caused