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Case Report

Corticosteroid-binding Globulin Dysfunction Due to Homozygous *SERPINA6* Lyon Variant in a Pediatric Patient

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Abstract

Corticosteroid binding globulin (CBG) deficiency is a rare disorder with poorly understood pathophysiology and variable presentations. We report on a pediatric patient presenting with poor growth and delayed puberty who was diagnosed initially with primary adrenal insufficiency following 2 failed ATCH stimulation tests with normal CBG and low stimulated salivary (free) cortisol. Genetic testing demonstrated a homozygous *SERPINA6* variant known as CBG Lyon. The patient's 2 siblings were later diagnosed with the same homozygous variant but were asymptomatic with normal stimulated salivary cortisol. CBG deficiency or dysfunction should be considered in patients with unexplained adrenal insufficiency. Further research is needed to better understand CBG's role in cortisol physiology.

Key Words: corticosteroid-binding globulin, corticosteroid-binding globulin deficiency, CBG, adrenal insufficiency

Abbreviations: CBG, corticosteroid-binding globulin; CDGP, constitutional delay of growth and puberty.

Introduction

Cortisol is a hydrophobic molecule requiring protein binding for transport in the blood. Eighty to 90% of cortisol is bound to corticosteroid-binding globulin (CBG), while 10% to 15% is bound to albumin, leaving approximately 5% unbound [1]. CBG is a glycoprotein encoded by the gene serine protease inhibitor A6 (*SERPINA6*) [1]. CBG acts both as a reservoir for cortisol and a modulator of cortisol release. While free cortisol is the main determinant of cortisol effects, CBG is also thought to play a biological role, though one that is less critical and poorly understood [1].

Congenital CBG deficiency is a rare disorder with 10 *SERPINA6* gene variants described in the literature [2, 3]. Clinical presentations include asthenia, chronic fatigue, chronic pain, and relative hypotension [3], though some patients are asymptomatic [4].

The CBG Lyon variant is associated with significantly decreased cortisol binding affinity and low CBG levels, with both features being more pronounced in homozygotes vs heterozygotes [4, 5].

We report on the first pediatric patient with homozygous CBG Lyon along with testing and clinical outcomes of the proband's parents and 5 siblings.

Case Presentation

A 13-year, 9-month-old boy was referred for short stature. The growth chart demonstrated steady linear growth between the 3rd and 10th percentiles from 9.5 to 12 years, with a fall to below the 3rd percentile after 13.5 years (growth velocity 2.9 cm/year). A review of systems was negative. There was no exogenous glucocorticoid exposure. Past medical history included only Thalassemia trait. The father and brother had a history of constitutional delay of growth and puberty (CDGP). There was no known history of adrenal insufficiency. Parents are second cousins from Syria.

Height was 145.2 cm ($Z = -2.19$) and body mass index 17.22 kg/m^2 ($Z = -0.81$). There was no hyperpigmentation. Puberty was early Tanner 2 (testes 4 mL).

Diagnostic Assessment

Bone age was 11 years at a chronological age of 13 years, 9-months. Workup demonstrated a low morning (8:47am) serum cortisol of 3.26 µg/dL [International Standard of Units (SI): 90 nmol/L] (reference range, 4.82-19.47 µg/dL [SI: 133-537 nmol/L]) (Elecsys II [Roche Diagnostics] immunoassay). Cortisol was tested given poor growth velocity. ACTH stimulation testing (cosyntropin 250 mcg) demonstrated low baseline (8:35am) cortisol 3.19 µg/dL (SI: 88 nmol/L) and cortisol peak 7.43 µg/dL (SI: 205 nmol/L) at 60 minutes (reference range, ≥18.13 µg/dL [SI: ≥500 nmol/L]). Baseline ACTH was mildly elevated at 109 pg/mL (SI: 24 pmol/L) (reference range, ≤81.74 pg/mL [SI: ≤18 pmol/L]). CBG was 2.8 mg/dL (reference range, 1.9-4.5 mg/dL).

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ACTH stimulation testing was repeated after 10 months as the initial abnormal result did not fit with the clinical picture. Repeat testing remained abnormal with baseline cortisol (8:40 AM) 4.42 µg/dL (SI: 122 nmol/L) and peak cortisol 11.71 µg/dL (SI: 323 nmol/L). Repeat baseline ACTH was 81.74 pg/mL (SI: 18 pmol/L).

Adrenal antibodies were negative. Serum albumin, very long chain fatty acids, electrolytes, renin, and pituitary hormones including GH and LH-releasing hormone stimulation testing, were normal. Magnetic resonance imaging of the head was normal apart from the pituitary gland being small for age.

A 3-gene custom sequencing panel (Prevention Genetics, Wisconsin, USA) demonstrated a homozygous, likely pathogenic variant in *SERPINA6* (c.1165G > A, p.Asp389Asn) in the proband; both parents were heterozygous for the variant [6].

Following the genetic diagnosis, an ACTH stimulation test was performed with concurrent measurements of serum and salivary cortisol. Baseline serum cortisol was 1.12 µg/dL (SI: 31 nmol/L), and salivary cortisol was 0.29 µg/dL (SI: 7.9 nmol/L) (reference range, 0.1-0.18 µg/dL [SI: 2.76-5 nmol/L]), with peak serum cortisol 3.77 µg/dL (SI: 104 nmol/L) and salivary cortisol 0.57 µg/dL (SI: 15.6 nmol/L) (reference range, >0.84 µg/dL [SI: >23.2 nmol/L] [7]). The patient was diagnosed with mild adrenal insufficiency based on low peak salivary (free) cortisol, with suspicion of CBG dysfunction due to homozygous CBG Lyon variant (Fig. 1).

Treatment

Once-daily morning physiological hydrocortisone replacement (with stress dosing as needed) was initiated following the first abnormal ACTH stimulation test at 8.3 mg/m^2/day. Once-daily dosing was provided due to lack of symptoms and diagnostic clarity. Treatment was continued following the genetic diagnosis given low peak salivary cortisol on stimulation testing, ongoing poor growth velocity, and delayed puberty.

On several occasions, the patient independently discontinued hydrocortisone replacement and, on 2 of these occasions, experienced symptoms of adrenal insufficiency (headache, decreased energy, nausea, abdominal pain), which resolved after restarting hydrocortisone. At the time of repeat ACTH stimulation testing, he had reinitiated once-daily physiological hydrocortisone for 1 month. Hydrocortisone was held for 24 hours prior to testing. Given his physiological dose of hydrocortisone replacement, first morning administration, and overall poor adherence, symptoms and the results of his subsequent ACTH stimulation testing were not felt to be due to adrenal suppression or adrenal withdrawal.

Given the complexity of the case, a second opinion was obtained from a quaternary care center in our region, which substantiated the diagnosis and management plan.

Outcome and Follow-up

Initially there was no improvement in growth and puberty. Growth velocity eventually improved, and puberty progressed. Given the observed clinical course and the fluctuation of symptoms over time without definitive correlation to treatment adherence, it proved challenging to ascertain whether poor growth velocity was attributable solely to CDGP or if it was exacerbated by CBG dysfunction. At the most recent clinical assessment, growth and puberty had advanced appropriately, and the patient remained asymptomatic on physiological hydrocortisone therapy (Fig. 2).

The patient's family underwent genetic testing. Both parents and 2 siblings were found to be heterozygous for CBG Lyon; all were asymptomatic. One sibling was wildtype (no CBG Lyon variant). Two of the proband's brothers (siblings 1 and 2) were found to be homozygous for CBG Lyon (Fig. 3).

Sibling 1 (15-year-old male) was asymptomatic with normal growth and puberty. ACTH stimulation testing with concurrent serum and salivary cortisol measurements demonstrated low baseline and stimulated serum cortisol and high baseline and stimulated salivary cortisol (Fig. 4). Baseline ACTH was 71.75 pg/mL (SI: 15.8 pmol/L) (reference range, 7.27-63.12 pg/mL [SI: 1.6-13.9 pmol/L]). CBG was 2.7 mg/dL. Hydrocortisone replacement was not initiated.

Sibling 2 (13-year-old male) had symptoms of fatigue and orthostatic dizziness. He had normal growth and puberty. ACTH stimulation testing with concurrent serum and salivary cortisol measurements demonstrated low baseline and stimulated serum cortisol and high baseline and normal stimulated salivary cortisol (Fig. 5). Baseline ACTH was 30.88 pg/mL (SI: 6.8 pmol/L). CBG was 2.1 mg/dL. Hydrocortisone replacement was not initiated.

Discussion

We report the first case of a pediatric patient presenting with poor growth velocity who was found to have a homozygous

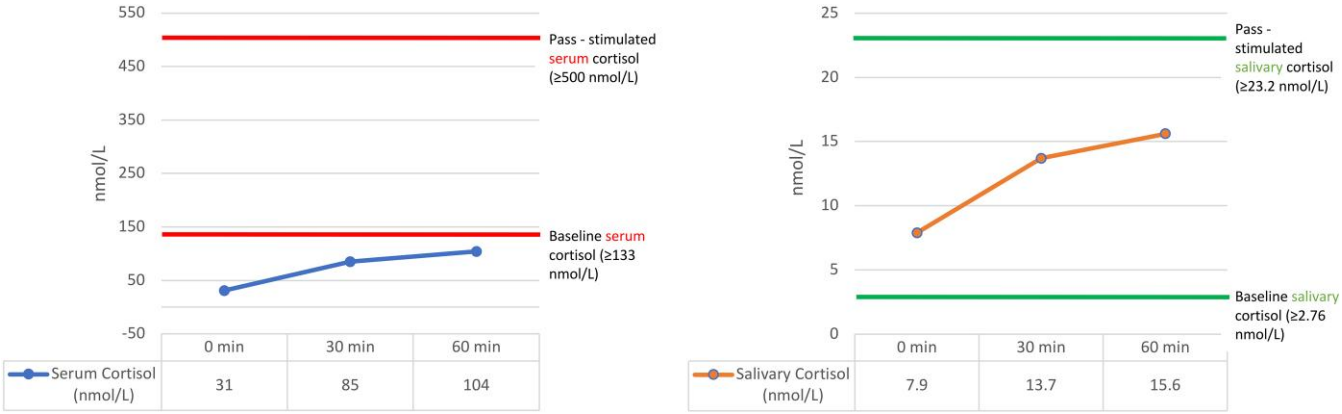


Figure 1. Proband: Standard-dose ACTH stimulation test (cosyntropin 250 mcg).

CBG Lyon variant, along with his 2 siblings with the same homozygous genotype. All 3 patients had baseline salivary cortisol levels above the normal reference range from our laboratory. However, it is important to note that the reference ranges for morning salivary cortisol are not validated for adrenal insufficiency screening. While CBG deficiency has been reported to impact total cortisol (secondary to decreased or dysfunction of binding globulins), a normal rise in stimulated

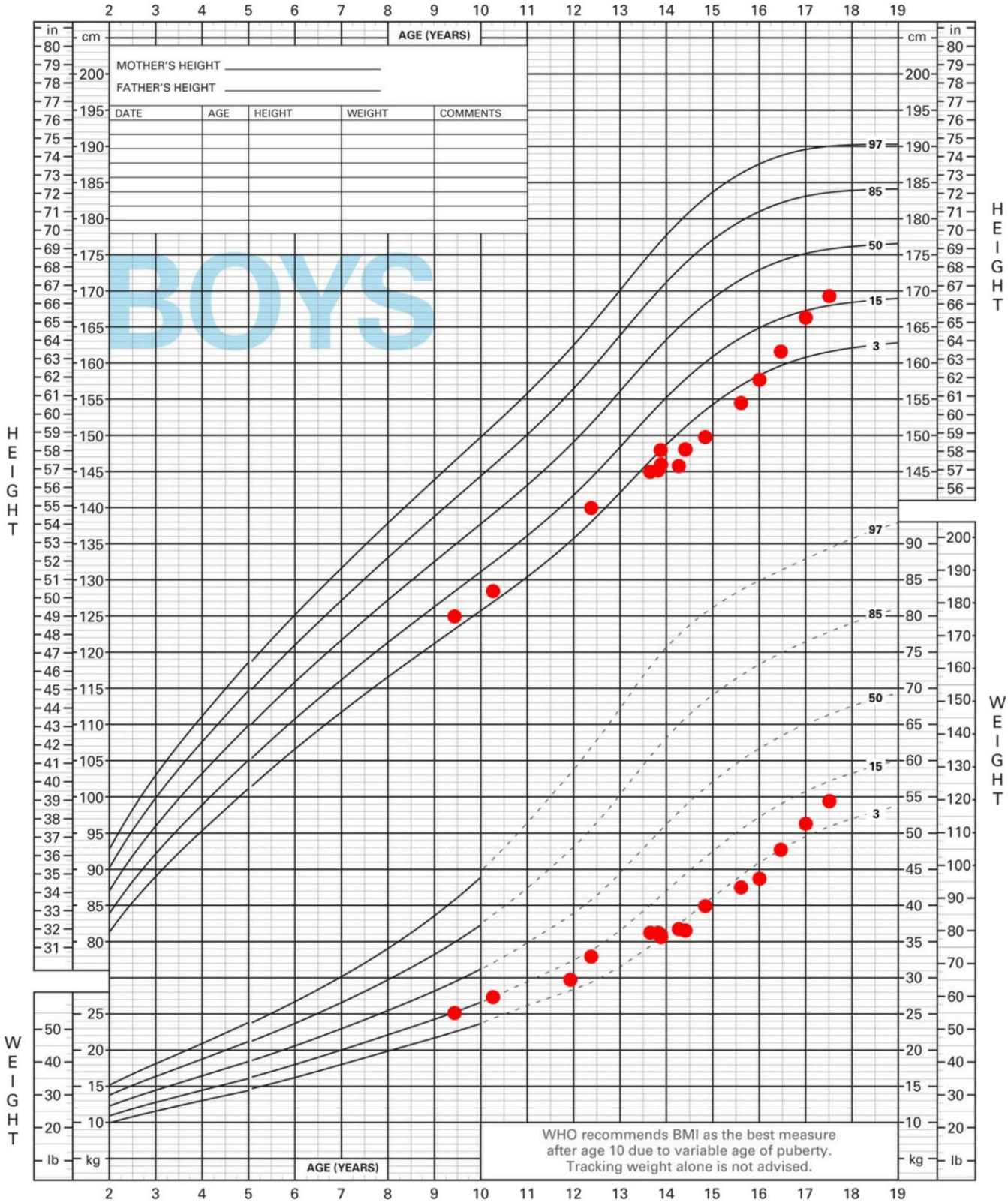
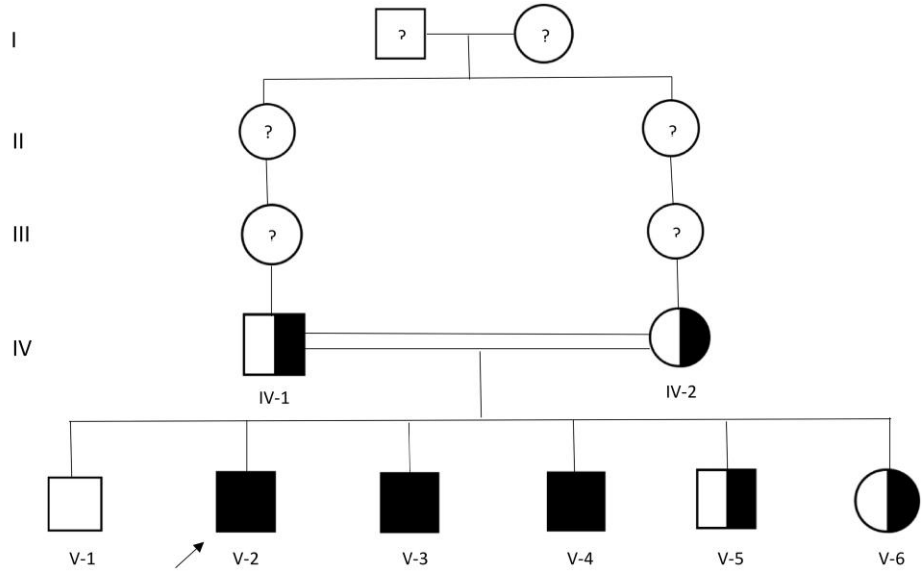


Figure 2. Growth points plotted on the Canadian Pediatric Endocrine Group growth chart using the World Health Organization reference data (https://cpeg-gcep.net/content/who-growth-chart-plotter-app). Growth chart from the Canadian Pediatric Endocrine Society.



	Proband	Sibling 1	Sibling 2
Short Stature	+	-	-
Delayed Puberty	+	-	-
Fatigue/Dizziness	-	-	+
Baseline ACTH in pmol/L	24 (H)[1]	15.8 (N)[2]	6.8 (N)[2]
CBG level in mg/dL (reference range, 1.9-4.5)	2.8	2.7	2.1

[1]reference range, ≤18 pmol/L
[2]reference range, 1.6-13.9 pmol/L

Figure 3. Pedigree along with associated signs, symptoms, and key laboratory findings of the proband and siblings with homozygous CBG Lyon variants. Abbreviation: CBG, corticosteroid binding globulin.

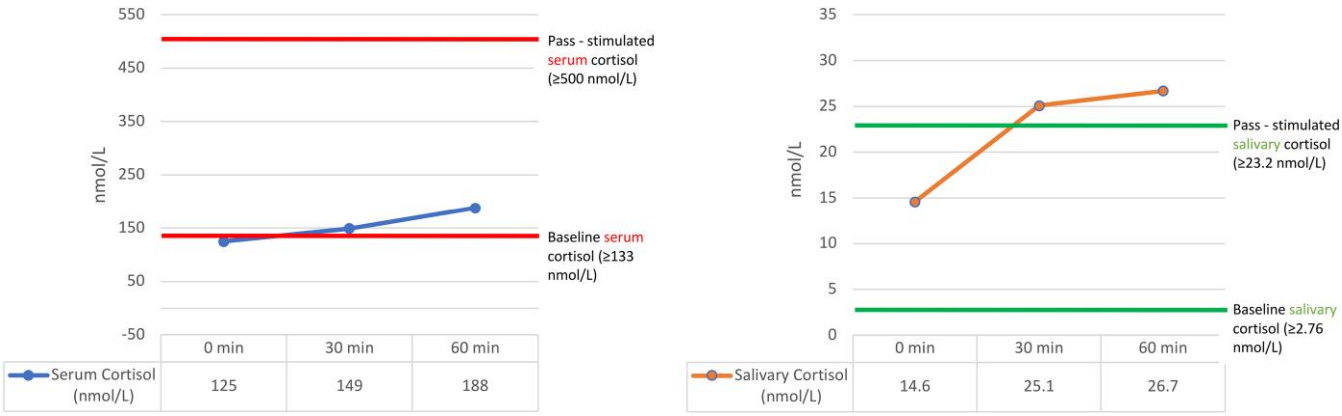


Figure 4. Sibling 1: Standard-dose ACTH stimulation test (cosyntropin 250 mcg).

salivary cortisol levels has been previously reported in those with rare *SERPINA6* variants [8]. While there are no validated stimulated pediatric salivary cortisol thresholds, compared to adult normative data, our patient had suboptimal stimulated levels [7]. The low stimulated free cortisol levels led us to consider mild adrenal insufficiency secondary to CBG dysfunction as the potential etiology of our patient's findings, though the lack of significant ACTH elevation argues against this. It is possible that our patient's symptoms related directly to CBG dysfunction given the poorly understood biological roles of CBG and previous reports of nonspecific symptoms in patients with CBG deficiency who typically do not have true adrenal insufficiency [1].

Our patient presented with poor linear growth and delayed puberty which improved after hydrocortisone therapy. While the presentation may have been secondary to CDGP, especially given a family history of CDGP, the poor growth velocity for bone age did not clearly fit with this condition, which is described as having a normal growth rate for bone age [9]. Given that poor linear growth can be a presenting sign in some forms of adrenal insufficiency and that previously reported cases of CBG deficiency have had symptoms that mimicked those of

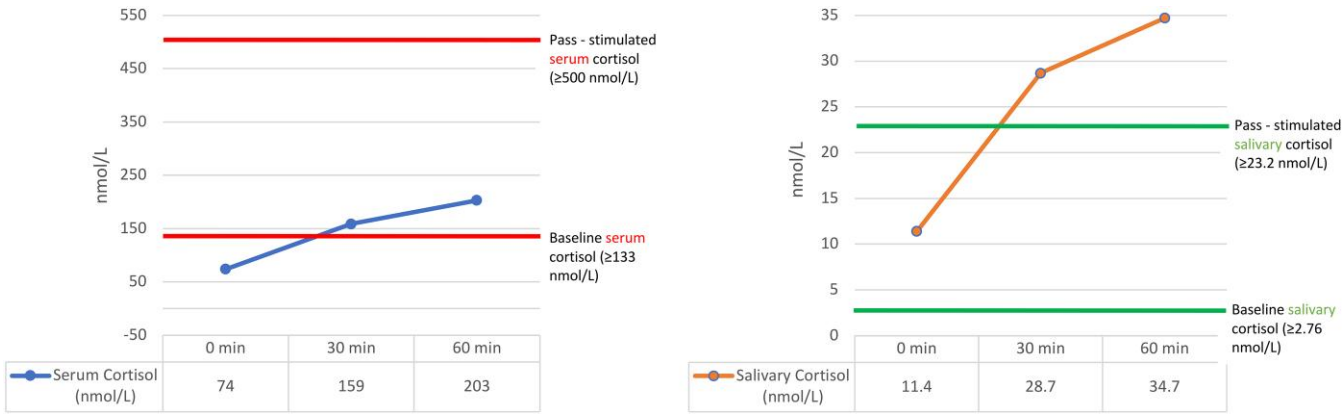


Figure 5. Sibling 2: Standard-dose ACTH stimulation test (cosyntropin 250 mcg).

adrenal insufficiency [2, 4, 5, 8, 10], poor linear growth may be considered as a possible sign of CBG deficiency or dysfunction in children [11], though this association requires further study.

Our patient had a normal CBG level when measured on immunoassay. Although previous reports have demonstrated low CBG levels, significantly reduced CBG binding capacity has been demonstrated to be the key feature of the CBG Lyon variant [5]. We postulate that our patient has qualitative CBG dysfunction. Previous reports have suggested variable expressivity and/or incomplete penetrance of the CBG Lyon homozygous variant, which may explain why our patient had normal CBG levels in contrast to previous reports of low or borderline-low CBG levels [5, 12].

In the only 2 previous case reports of individuals with homozygous CBG Lyon [4, 5], 2 adult women presented with fatigue and weakness, while 1 of the probands had an affected asymptomatic sister. The symptomatic patients had low basal and stimulated total serum cortisol but normal free cortisol; all 3 had low CBG and significantly reduced CBG binding capacity [4, 5].

There are only 2 reported pediatric patients with *SERPINA6* variants [2, 10]. The first, a 9-year-old male with CBG Santiago, presented with chronic fatigue, headaches, weakness, and parental concern for short stature (z-score −0.79) with normal growth velocity and puberty. Biochemical testing ruled out adrenal insufficiency. A trial of hydrocortisone following genetic diagnosis did not improve symptoms [10]. The second, a 7-year-old male with CBG Montevideo, presented as a neonate with hypoglycemic seizures associated with total hypocortisolemia (but normal free cortisol), which responded to hydrocortisone treatment. The patient continued to have exercise intolerance, episodic ketotic hypoglycemia, and inappropriately low total serum cortisol throughout childhood [2]. Given that the patient was symptomatic despite normal free cortisol, the authors postulated an additional role for CBG in cortisol regulation of hepatic glucose homeostasis and cortisol-brain communication [2]. We are unaware of other reports of ongoing hydrocortisone therapy for CBG deficiency.

Traditionally, CBG was considered to be mainly for cortisol transport with unbound (free) hormone providing the biological activity [3]; however, cases of symptomatic individuals with CBG deficiency/dysfunction suggest otherwise [2, 4, 5, 10]. We postulate that the relative increase in free cortisol in those with CBG deficiency may not fully compensate for the lower total cortisol and may lead to symptoms of mild adrenal insufficiency in more severe variants. Ongoing reporting and further characterization of patients with CBG deficiency and dysfunction are required to better understand the etiology of symptoms and the role for cortisol replacement. Our case brings novel insights to this rare condition, and further research is required to understand the implications of CBG Lyon variant.

Learning Points

- In pediatric patients presenting with unexplained adrenal insufficiency, CBG deficiency/dysfunction should be considered even if CBG levels are within the normal range.
- Measurement of free cortisol is essential to understand the cortisol status of patients with CBG deficiency/dysfunction. Further research is needed to develop validated reference ranges for pediatric populations.
- Individuals homozygous for CBG Lyon can have significant variability in presentation. Further research into the biological role of CBG is required.
- It is yet to be determined if poor growth and delayed puberty are signs of CBG deficiency/dysfunction. A trial of glucocorticoid replacement may be considered on an individual basis to manage symptomatic CBG deficiency/dysfunction until the entity is further understood.

Contributors

All authors made individual contributions to authorship. M.R.J., C.Z., M.T.C., and A.A. were involved in the diagnosis of the patient. M.R.J. and C.Z. were involved in the management of the patient. M.R.J. was involved in the manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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