The first case of primary generalized glucocorticoid resistance in Serbia in an 8-year-old boy with G679S mutation of the NR3C1 gene

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Background

Primary generalized glucocorticoid resistance (PGGR) is a rare genetic condition characterized by generalized, partial target-tissue insensitivity to glucocorticoids, which leads to compensatory activation of the hypothalamic-pituitary-adrenal axis and hypersecretion of adrenocorticotrophic hormone (ACTH) in the systemic circulation. The latter results in adrenocortical hyperplasia, increased cortisol secretion, increased production of adrenal steroids with mineralocorticoid and androgenic activity.

PGGR is primarily caused by mutations in the NR3C1 gene, which generally result in a defective glucocorticoid receptor and decreased tissue responsiveness to glucocorticoids.

Case presentation

An 8.5-year-old boy was hospitalized because of precocious puberty and arterial hypertension. Over the last year, the appearance of pubic hair and gynecomastia were noted.

At the local centre, high levels of ACTH, cortisol, testosterone and 24-hour urinary free cortisol excretion were noted, as well as hypokalemia, alkalosis and pubertal response during LH-RH test. Abdominal CT scan was normal, while head MRI showed pituitary microadenoma of 3 mm in diameter. Patient was started on dexamethasone (1 mg per day) and GnRH agonist therapy. Hypertension was treated by spironolactone, propranolol and captopril therapy.

On admission to our hospital he was tall (90th percentile) and obese (BMI 22.2 kg/m² at 97th percentile) with arterial hypertension. No striae were noted and obesity was not centripetal in pattern. Serum cortisol levels were high with preserved diurnal variation (at 8 AM 2557 nmol/L; at 10 PM 580 nmol/L). Morning serum cortisol was suppressed only after high-dose dexamethasone test.

Highly elevated ACTH level was noted 443.9 pg/mL (ref. range 7.2-63.3), as well as elevated levels of 17-hydroxyprogesterone 19.9 nmol/L (0.5-3.1), DHEA 19.9 μg/ml (0.31-3.4), DHEAS 50 μmol/l (0.34-2.16), 11-deoxycorticosterone 111 ng/100 ml (2-34) and testosterone 3.8 nmol/l (ref. range below 0.1). Urinary catecholamines, metanephrines and normetanephrines were normal.

According to the clinical findings and the results of the laboratory investigation the diagnosis of PGGR was established.

Boy and his parents underwent genetic investigation. The entire coding region, of the human glucocorticoid receptor gene (hGR, NR3C1) and the intron/exon junctions, were amplified by PCR and bi-directionally sequenced.

The boy was found to be homozygote for the mutation G679S in exon 8 of the NR3C1 gene. The parents were found to be heterozygotes for the mutation G679S in exon 8 of the NR3C1 gene.

This mutation is a known disease causing mutation and is known to be associated with PGGR.

Conclusions

We are presenting the first case of PGGR diagnosed in Serbia. Despite the fact that PGGR is a very rare disease, it must be considered in every child with precocious pubarche, especially if associated with hypertension.

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The author disclosed no conflict of interest

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