Very high DHEAS in serum of an overweight female adolescent without a tumor

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57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

Poster number: P2-P025

Case report:

- A female adolescent (18.5 yrs) with overweight (BMI 29.0 kg/m^2).
- No signs of hyperandogensim or hypercortisolism, were present.
- Very high DHEAS serum levels were found. DHEA, ACTH, LH, FSH, testosterone, cortisol, androstenedione, 17-OH progesterone, TSH, fT4 were within the normal range.

Background:

- DHEAS excess may be due to the presence of either an ovarian or an adrenal DHEAS-producing tumor.
- Steroid sulfatase (STS) hydrolyses alkyl and aryl steroid sulfates to their unconjugated forms. STS deficiency was suspected in our patient although ichthyosis was absent.
- DHEAS is transported through the cell membrane by several transmembrane channels.

Methods:

- Hormone levels in blood and urine were measured using automated chemiluminescence assay and GCMS.
- Dexamethasone suppression test was used to suppress DHEA and DHEAS.
- Sonographic and MRT investigations were used to search for an adrenal or ovarian tumor.
- Sequence analysis and MLPA of *STS* was performed.
- STS activity assay was performed using patient's leukocytes.
- Exon-spanning PCR and sequence analysis were performed for the DHEAS-membrane-transporter-genes.

Results:

Patient's serum hormone data as detected by immunoassay

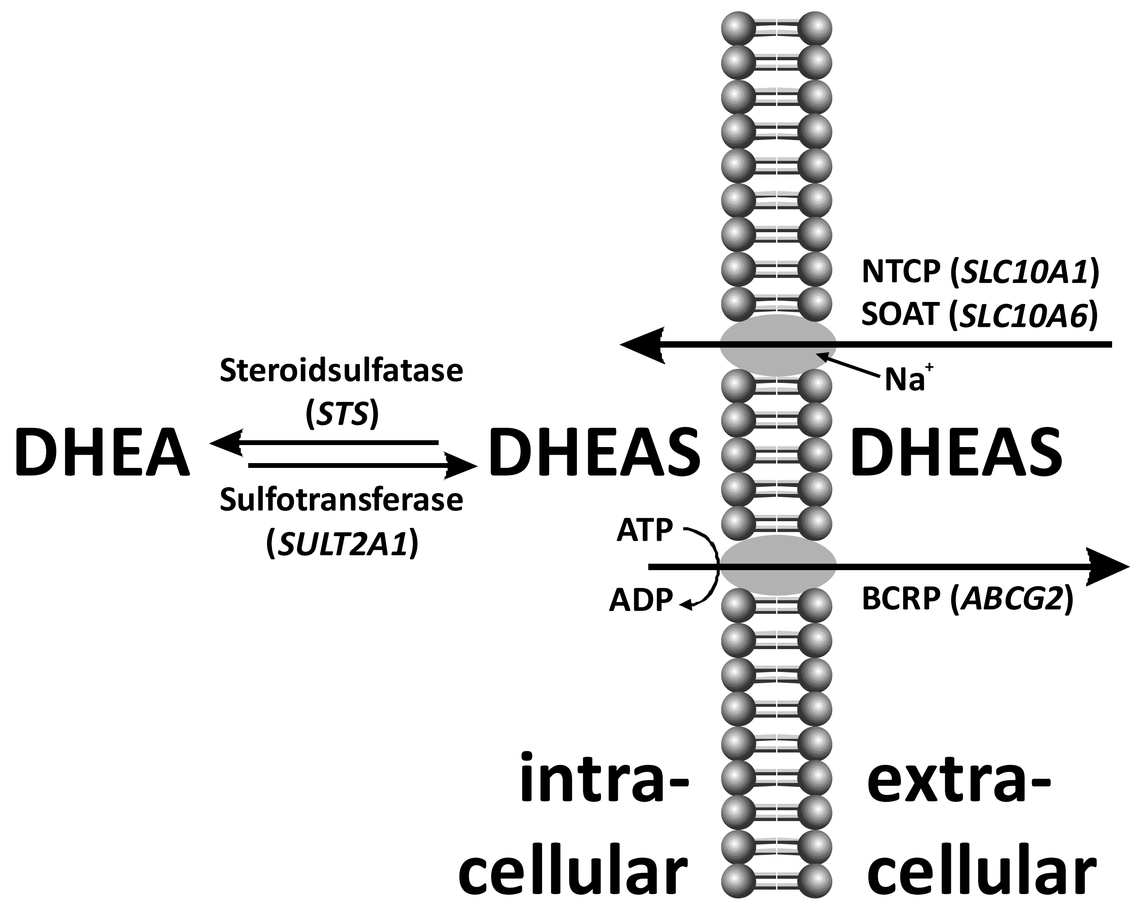
Serum analyte	Unit	Value	Reference range
DHEAS basal	ng/ml	7,546; 8,835*	1,450 - 4,000
after dexa suppression	ng/ml	1,199	
DHEA basal	ng/dl	443	200 - 750
after dexa suppression	ng/dl	144	
Androstendione	nmol/L	10	<12
Testosterone	ng/dl	28	<45
ACTH	pmol/L	4.8	<11

* range of four measurements

Increased patient's level of sulfated steroids as detected by GCMS

Compound	Concentration [ng/mL]	Reference range
Cholesterol sulfate	1171.4	500-2000
Pregnenolone sulfate	121.7 increased	15-90
17-hydroxypregnenolone sulfate	25.3 increased	2-13
16-α-hydroxy -DHEAS	294.0 increased	30-180
DHEAS	5085.2 increased	800-3500
Androstenediol -3-sulfate	293.8 increased	50-275
Androsterone sulfate	3366.7 increased	250-1500
Epiandrosterone sulfate	772.7 increased	100-500

- Sonographic and MRT investigations, as well as the results from the dexamethasone suppression test abolished the hypothesis that an adrenal or ovarian tumor was causative.
- Sequence analysis and MLPA of STS revealed a heterozygote single-base substitution (g.117217G>T) that results in a nonsense mutation at codon 173 (p.G173X). This mutation predicts a truncation of the carboxyl region of the STS enzyme that is implicated in substrate binding. In line with the genetic data, the bioassay revealed normal enzyme activity in patient's leukocytes.
- Sequence analysis revealed a heterozygous Q141K variant for BCRP. This variant has in its homozygous state previously been associated with reduced efflux transport activity.



Conclusions

A novel heterozygous nonsense mutation in the steroid sulfatase gene and a known heterozygous missense variant of the steroid sulfate efflux transporter were found in this patient. The combination of the two heterozygous mutations could possibly together explain the observed high levels of DHEAS and some other sulfated steroids.

Disclosure statement: The authors declare that there is no conflict of interests.

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