NEWBORN SCREENING FOR CAH: SHOULD WE WORRY MORE ABOUT FALSE POSITIVES OR FALSE NEGATIVES?

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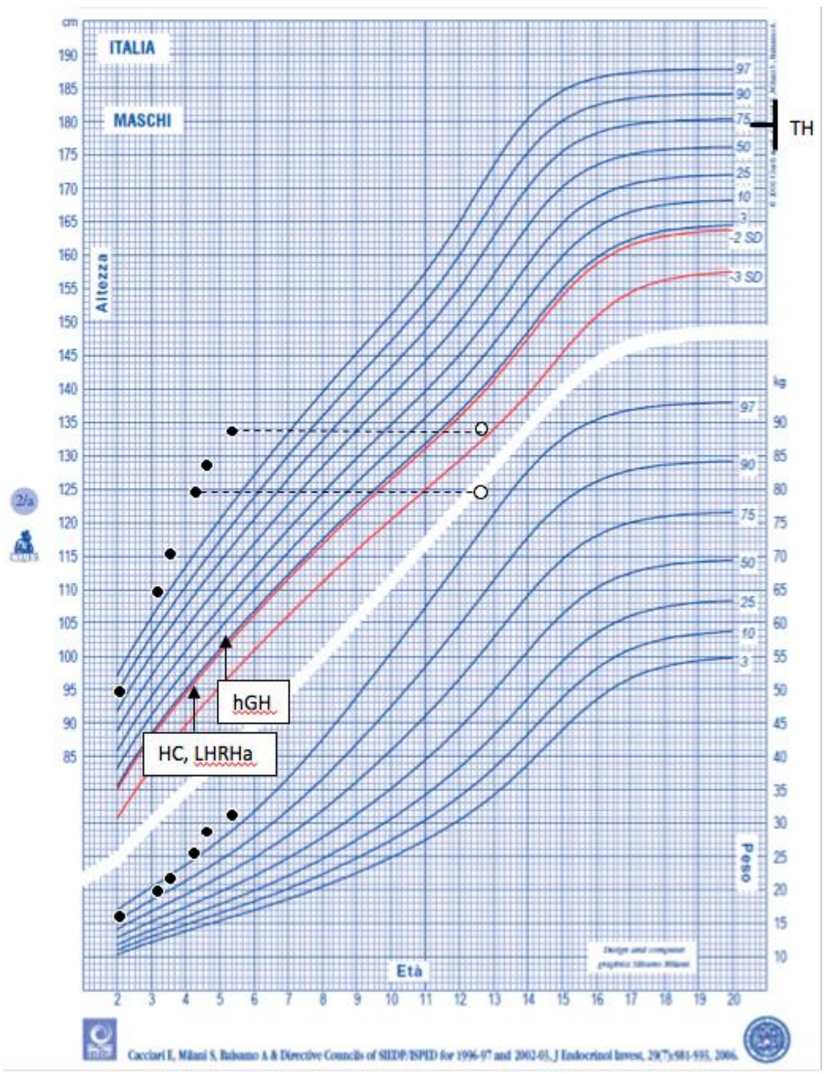
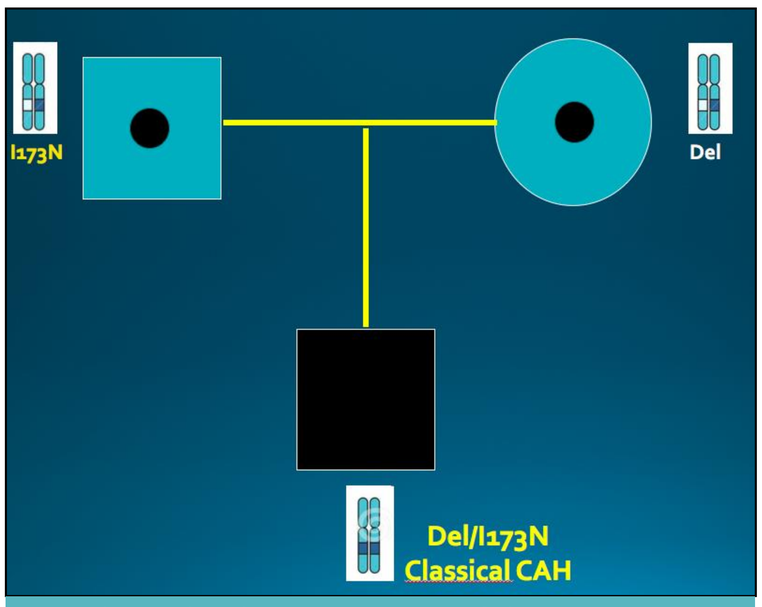
Background

Newborn screening for congenital adrenal hyperplasia (CAH) is based on the determination of 17OHP on blood and its need is confirmed by the most recent guidelines on the subject. Among its disadvantages, it is well known the high frequency of false-positives, in particular in premature babies and those born small for gestational age. However, there are a number of subjects who are false-negatives (FN), with the risk of late diagnosis and development of complications.





From the molecular investigation of the CYP21A2 gene, the patient resulted hemizygous for the p.I173N variant

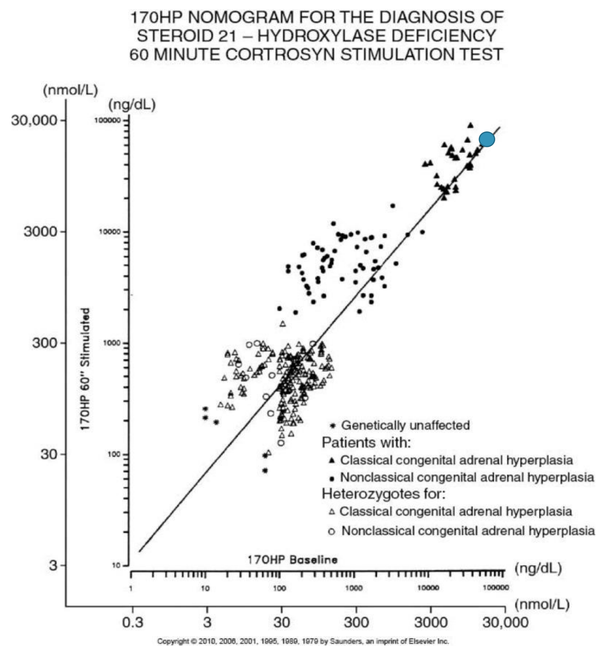
Case report

A 4-year-old boy presented with pubic hair, body odor and acne noted one year earlier. Height was 125.1 cm (+3.85 SDS, target height +0,70 SDS). He was Tanner stage 2 (G2PH3, testicular volume 4 ml bilaterally). BP was 95/59 mmHg. Bone age was 12-13 years.

He was recalled for CAH screening performed at 3 days of life (17OHP 35 nmol/l, n.v.<18), showing normal values of 17OHP at 6 days of life (8 nmol/l). He was a first-born from unrelated parents without significant illnesses. Pregnancy and vital parameters at birth were regular; birth weight was 3660 g.

Due to the clinical picture and blood tests (Table), a diagnosis of classical CAH complicated by a central precocious puberty was made.

	PATIENT	N.V.
17OHP 0' 17OHP 60'	>19 ug/l (158 ng/ml) >19 ug/l (218 ng/ml)	0.2-2.9
CORTISOL 0' CORTISOL 60'	71 ug/l 71 ug/l	>180
ACTH	67.2 ng/l	7.2-63.3
DHEAS	7.3 umol/l	0.08-2.31
ANDROSTENEDIONE	8.6 ug/l	0.3-3.1
TESTOSTERONE	3.46 nmol/l	0.1-1.12
ALDOSTERONE	453 ng/l	12-240
RENIN	303.6 mUI/l	2.8-39
SODIUM	139 mmol/l	136-145
POTASSIUM	4.7	3.5-5.1
LH 0' LH PEAK	<0.1 UI/l 5.3 U/l	<5
FSH 0' FSH PEAK	0.6 UI/l 1.9 UI/l	



Treatment and follow up

The following treatments were started:

- Replacement therapy with hydrocortisone and fludrocortisone
- Puberty blocking therapy
- hGH to improve height prognosis.

	4.2 years	4.7 years	5 years	5.5 years
Stature cm (SDS)	125.1 (+3.85)	128.1 (+4)	130.6 (+3.82)	134.4 (+3.84)
Weight kg (SDS)	25.1 (+2)	29.5 (+2,56)	31.5 (+2,83)	31.8 (+2.21)
Δ4Androst mcg/l (0.2-3.1)	8.6	5.6	3.3	4.4
Testosterone nmol/l	3.46	1.45	0.59	1.12
Renin mUI/l (4.4-46)	303	157	56.2	103
HC mg/mq/day		12.5	13.6	14.9

Discussion

Newborn screening has still limitations in the diagnosis of CAH. FN are produced for reasons still unclear, including issues in timing and/or sensibility of laboratory tests. FN are underestimated, also due to the lack of an effective reporting system for patients with late diagnosis; furthermore, they are underreported in literature (Votava et al,2005; Schreiner et al,2008; Sarafoglou et al,2012). Therefore, pediatricians should be aware that a negative newborn screening does not rule out the manifestation of classical CAH during later stages of life.