

Congenital Adrenal Hyperplasia: a Missed Diagnosis in Egypt

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Congenital adrenal hyperplasia is a common inherited form of adrenal insufficiency. About 95 percent of cases are caused by 21-hydroxylase deficiency, of which about 75 percent are salt losers. Severely affected girls may be mistaken as boys at birth, whereas affected boys have no genital ambiguity but they may die silently in salt losing crisis. Moreover, the uninterrupted androgen excess secretion leads to pseudo precocious puberty in both sexes with premature epiphyseal fusion and eventual short final adult stature .

Congenital adrenal hyperplasia in Sweden (1969 –1986), in the era before neonatal screening program (Thilen and Larsson, 1990).

143 patients with CAH (retrospective study)

- 93 salt losers:
All diagnosed < 3 mo of age
2 died, many were critically ill during first weeks of life.
- 50 simple virilizing:
38 girls with genital ambiguity, 15 wrongly assigned as boys in their first 40 ds.

The mean age of diagnosis in patients without genital ambiguity was 17 mo.

Since the incidence of classic CAH worldwide is about 1 in 10,000 of total birth, this amounts to a substantial number of potentially preventable infant deaths . Neonatal screening programs have achieved their goals where the mortality from adrenal crisis mainly in boys, who have no outward signs of the disease, is being prevented.

What is the situation in Egypt?

Incidence of CAH in Egypt is not yet determined. Neonatal screening program is recently implemented, however, it is exclusively confined to congenital hypothyroidism.

Incidence is expected to be high, as Egypt like most Arab countries, has increased rate of consanguineous marriage (33%) (Hafez ,1983).

Over the last few years, the DEMPU – Children Hospital , Cairo University- reported cases with CAH more frequently than before.

- Better public awareness of the problem of genital ambiguity
- Specialized centers are increased and are well recognized.

However, many of these cases are diagnosed late.

Problems of CAH encountered in Egypt

- Salt losing crises .
- Ambiguous sex determination
- Compromised adult stature
- Potential adrenal or pituitary tumors

Salt Losing Crisis

Diabetes Endocrine Metabolism Pediatric Unit (DEMPU), Cairo University Children Hospital

- Patients with salt losing crises are mainly admitted to ER, then to inpatient endocrine department.
- Endocrine inpatient department (March 2004 – October 2006)

176 patients with salt losing crises:

32 in 2004

53 in 2005

91 in 2006

Most < 3 months of age

Most are girls with genital ambiguity, however, 93 named as boys, while 83 named as girls.

How many boys died with unrecognized salt losing crisis?

Ambiguous Sex Determination

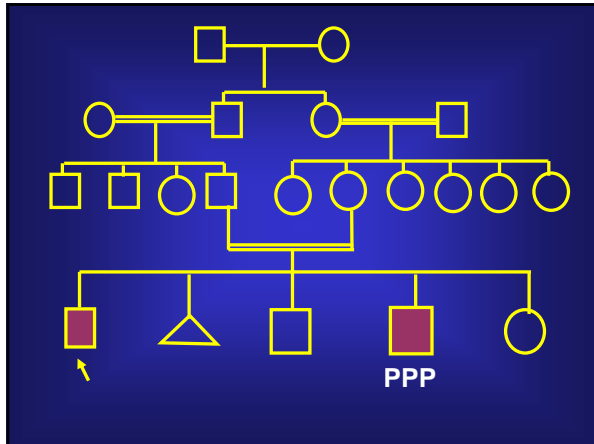
Patients

Six cases of virilizing CAH (21,OHD) with 46xx karyotype.

Diagnosis was profoundly delayed and compliance was bad.

Demography and anthropometry

- Locality : 2/3 from upper Egypt, rest from lower Egypt and Cairo.
- Family history : +ve consanguinity in all cases. Similar cases in one family (pseudo precocious puberty in a male).
- Repeated abortions and early infant deaths.



- All : genital ambiguity was recognized at birth.
- 2 cases were referred from urologist for bilateral cryptorchidism & pubarche (one case erroneously received HCG for cryptorchidism)
- In the 2nd year, all had accelerated growth, macropenis, pubic hair and pigmentation.
- 2 cases had highly suggestive history of salt losing crises .

Sex of rearing : all were named and reared as boys:

- * Typical male phenotype of external genitalia: phallus of normal length & girth, single urethral opening (prader stage IV-V), empty scrotum. Wrong diagnosis as a male with bilateral cryptorchidism inspite of the pseudoprecocious puberty.
- * Preference of male sex in Arab countries, more in upper Egypt, inspite of the genital ambiguity.
- * Having no male children in the family
- * wrong karyotype in one patient.
- * The advanced age at diagnosis.

Hormonal analysis :

* Cortisol	36.1 ± 18.5ug %	(23.0 - 49.2)
* Testosterone	3.9 ± 1.2 ng/ml	(2.4 - 5.4)
* 17 OH progesterone	43.7 ± 23.6 ng/ml	(10.5 - 75.5)
* Δ ₄ Androstenedione	19.5 ± 12.7 ng/ml	(10.0 - 40.0)
* DHEA	16.2 ± 8.8ng/ml	(1.9 - 24.0)
* DHEAs	108.9 ± 88.5 ug/dl	(1.4 - 200.0)

Genetic studies

- All : 46 xx Karyotype
- Molecular genetics in 2 patients :
Homozygous for splice I₂ deletion
Homozygous for Q318 X mutation

Anthropometry at onset of therapy

- CA 5.0 ± 0.7y (4.3 - 5.8)
- BA 13.1 ± 2.0y (10.5 -15.2)
- Height for CA SDS 3.8 ± 1.2 (2.0 - 5.0)
- Height for BA SDS - 4.9 ± 1.6 (-7.4 to -3.1)
- PAH 146.8 ± 1.3 (125.7- 159.5)
- PAH SDS - 2.5 ± 2.3 (- 6.0 to - 0.5)
- Wt SDS 2.5 ± 1.6 (0.6 - 4.1)
- BMI SDS 0.7 ± 0.4 (0.3 - 1.4)

Medical treatment

- **Hydrocortisone:**

Initial dose 15.5 ± 2.7 mg/m²/d (12.5-20.0)

Last dose 15.5 ± 2.9 mg/m²/d (12.0 – 20.0)

- **9- α fludrocortisone** for 2 cases (0.025- 0.05 mg/d)
- **LH RH-Analogue :**

One case at CA 6.5y and BA = 12y
Analogue was prescribed for another case ? vanished

Gender orientation

Sex role behavior

- Playmates preference.
- Family members preference
- Playing with toys: guns, football, aggression on provocation, dolls.
- Playing with babies.
- Preference of clothes.
- Abnormal sexual behavior.

Gender orientation of patients with CAH

- All are living their male life.
- Prefer male playing, but more tendency to electronic games, like to cuddle babies.
- Like male clothes
- More stuck to their homes (partly induced by their parents).
- Linked to a female caretaker (mother or older sister).
- No abnormal sexual behavior.

Failure of gender reversal

- Old age at diagnosis .
- Preference of boys.
- Locality : Upper Egypt.
- Social background (**Marriage, inheritance, religion, masculinity and femininity**)

Parents action

- Change of residency.
- Withdrawal from schools.
- Intention non - compliance.
- Refusal of any psychological assistance.

Surgical treatment

- **Urethroplasty** :
in 2 patients (6,10 y)
- **Panhysterectomy** :
in all patients
(5,7,10,10,11,18y).

School achievement

- 5 in school age, 3 only attending schools
- All have border line scores.

Long-term problems

- Continue male role : need for testosterone therapy for the sexual role.
- Bad compliance.
- Compromised adult stature.
- Potential adrenal or pituitary tumors.

Compromised Adult Stature.

Final Adult height In CAH

Attaining genetic height potential is often suboptimal in treated cases of CAH. Hyperandrogenism, treatment - induced hypercortisolism, or both, have direct effects. In the trial to correct for high androgens levels, we usually reach to an escalating high dose.

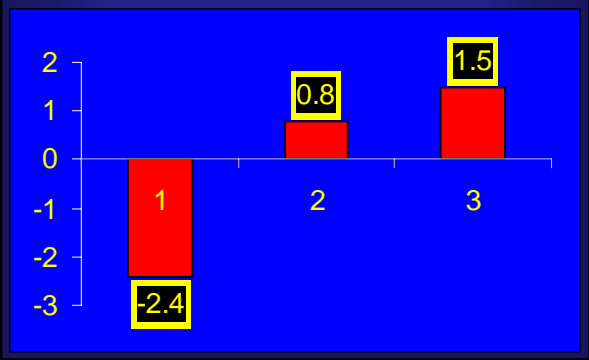
Aim of Work

We reported final height in 9 children with virilizing adrenal hyperplasia. Luteinizing-hormone releasing-hormone analogue (LHRH-An) was started either because of the occurrence of central precocious puberty on top of a pre-existing pseudo precocious puberty, or because of the marked advanced bone age with inevitable activation of the hypothalamic-hypophyseal pubertal mechanism.

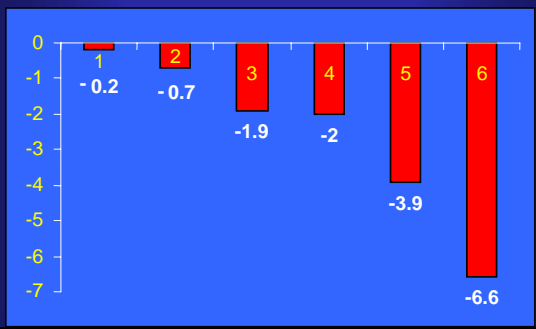
Patients characteristics:

- 9 Children; 3 Girls, 6 Boys
 - Mean age at presentation 4.3 ± 1.7 y
 - Mean age at start of treatment 7.2 ± 1.7 y, BA 11.9 ± 1.6 y
 - Treatment : LHRH - analogue (triptorelin depot, Ferring) 3.75mg i.m every 28 days
- Inclusion criteria
- i) Onset of central precocious puberty (LH- dominant response on LHRH stimulation)
 - ii) Marked advanced bone age with inevitable activation of the hypothalamic hypophyseal pubertal mechanism.

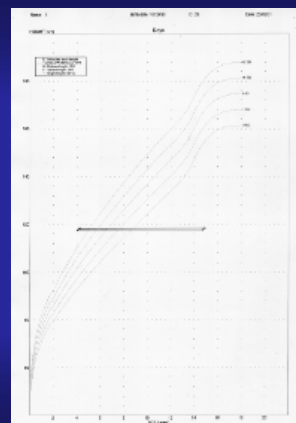
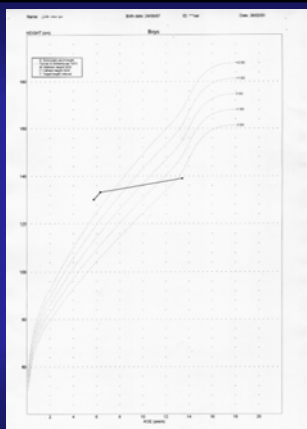
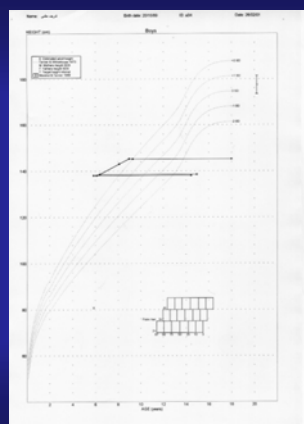
Final Height (SDS) in Girls with Virilizing Adrenal Hyperplasia

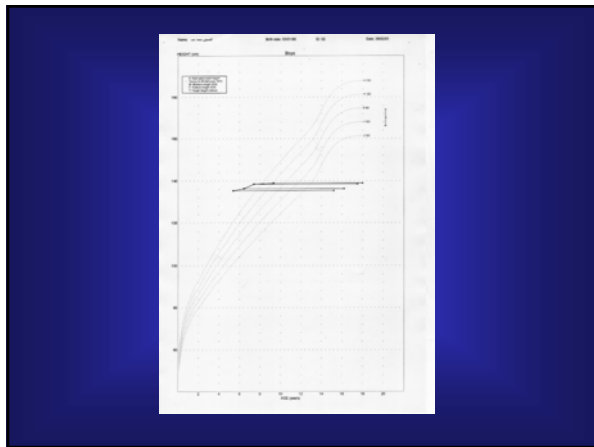
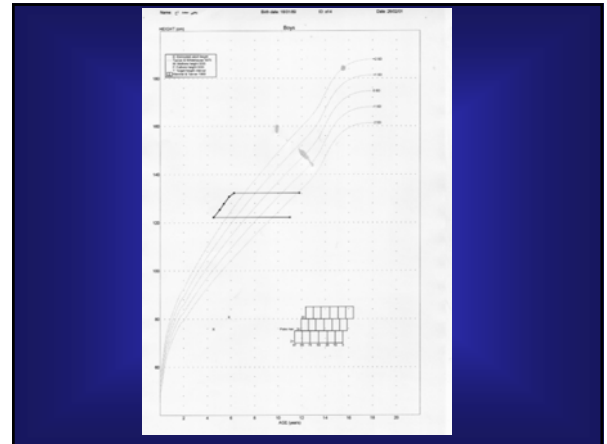
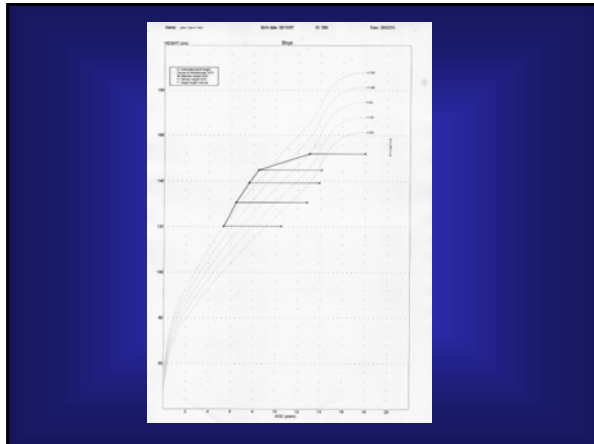


Final Height (SDS) in Boys with Virilizing Adrenal Hyperplasia



The better results reported in girls can be explained by the observation that most of males with pseudo-precocious puberty sought medical advice at an older age and with advanced skeletal maturity. This may be attributed to the fact that virilizing CAH in boys is slowly progressive, while in girls it presents early in life with genital ambiguity and progressive virilization.



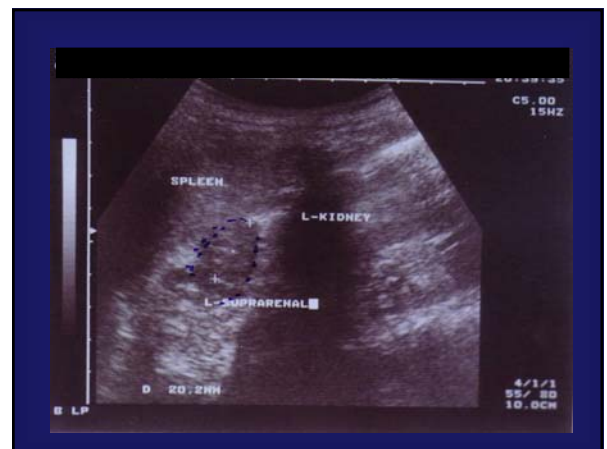


Potential Adrenal & Pituitary Tumours

Hormonal profile (Case no. 4)

Serum Cortisol	7.6	ug %
Serum 17 OH progesterone	> 20.0	ng/ml
$\Delta 4$ - Androstenedione	10.5	ng/ml
Serum testosterone	8.8	ng/ml
Serum estradiol	258	pg/ml

17 OHP > 200 ng/ml after further dilution





Conclusion & Recommendations

- Data emphasize the importance of early diagnosis and optimal control to insure satisfactory outcome.
- Late diagnosis of CAH, is a major problem among Egyptian patients. Inclusion of CAH in the current neonatal screening program in Egypt is strongly recommended . Avoidance of serious salt losing crises, correct gender assignment, decreased virilization, and reduced negative impact on psychosocial development and final height, are all possible benefits.

Thank You