FORUM: Congenital Adrenal Hyperplasia:

(In March, I saw these interesting letters on CAH, and wrote to members with email addresses, asking for their policy/experience re 17 OHP suppression in CAH. Would you like to add anything to this discussion? – Editor.)

Do patients with non-salt-losing form of CAH really need Florinef? In an 11 year old, with a renin of 2.5-3.1 ng/ml/hr, would anyone add Florinef to Hydrocortisone (HC) in a non-salt loser if the patient is Cushingoid from the HC dose (24 mg/m²/day) needed to suppress the 17-OHP at the desired level?

> During my training with Dr. Maria New at Cornell I learned to follow androgen levels, rather than 17-OHP, in patients with CAH. If the serum androgen levels are well suppressed, 17-OHP levels up to 1000 ng/dl are acceptable and patients will be less likely to develop iatrogenic Cushing's. Rosanna Fiallo Schurrer. Children's Hospital of Orange County.

> From my past experience with the Yupik Eskimos and Dr. Maria New's opinions, I would suggest Florinef for the nonsalt losers. It enables one to give less HC. With regards to pushing so much HC to make the patient Cushingoid to approach "desired" level of 17-OHP, I would caution you to not push 17-OHP into the "normal" range. It was Dr. New's feeling and others that trying to suppress the 17-OHP to normal would be overtreating the CAH patient. What range were you shooting for on 17-OHP? Are you seeing good growth rate? Joan MacCracken

These are the responses so far:

**PSN Menon, AIIMS, Delhi**: At the Pediatric Endocrine Clinic at AIIMS it is a routine practice to advise combination of HC and florinef to all patients with CAH including non-salt losers. This is based on the observations made by Dr Maria New and colleagues in their publications on follow-up of children with non-salt losers especially with reference to their growth. The addition of florinef also helps to reduce the total dose of HC from the cushingoid range. However the problem is different in our set up. HC and Florinef are both not usually available in the hospitals and pharmacies in Delhi and have to be imported from abroad or procured through nonofficial channels. This increases the cost of therapy and reduces compliance. Most poor patients are forced to continue with prednisolone alone without florinef. Pushing more of steroids to obtain a normal 17-OHP obviously leads to development of cushingoid features in very young infants and children. We have the added difficulty that these assays for 17-OHP and androgens are not routinely available in most of our hospitals and cities.

**Vijayalakshmi Bhatia, SGPGI**: I learnt exactly the same thing as McCracken and Fiallo, ie not to try to suppress 17-OHP levels but to follow androgens (and even better, to follow growth rate, weight, and bone age with androgen to help). However, in the literature there are numerous reputed people who mention 17-OHP. All I can say is that following androgens has served my teachers and me well in the past. Regarding Florinef, the classic teaching is that if renin is normal on HC dose of 10-15 mg/ sq m/ day (which should not produce Cushingoid effects), and on this dose of HC, if clinical and biochemical features suggest testosterone is suppressed, then Florinef is not needed. However, more often than not, renin may be high on this dose of HC, then Florinef should be added. Practically I did not have renin estimations here till last year, I used to give 0.05 mg Florinef, and look for hypertension, edema or hypokalemia to avoid unnecessary use of Florinef.

**Ravi Mehrotra, Apollo Hospital, Hyderabad**: It was interesting to read your query. I would consider doing Renin activity for every CAH and if elevated add fludrocortisone. I do feel activity of 2.5 is definitely high. The problem is Renin is not done commonly by the labs. As regarding monitoring, growth velocity and bone age are very important indicators. Normally we start with only prednisolone (HC is rarely available) in non salt wasting CAH, and follow up with androgens. If we find the patient is developing cushingoid features and Testosterone is still high, then we do add fludrocortisone. Another aspect is at 11 years patient may be in stage of normal adrenarche/puberty which would influence 17-OHP and Te levels. Accepted value of 17 OH P is 20 to 30 nmol/L. Is any body doing 11 de oxy cortisol? Please do let me know. I have a male hypertensive with peripheral precocity and low K.
**THE PELVIC ULTRASOUND IN CHILDHOOD**

*Ashok Khurana (From CAPENEWS 6.3, December 2002)*

**Uterus:** The average length of the neonatal uterus 1 day after birth is $3.2 \pm 0.5$ cm and the total volume $3.5 \pm 0.9$ ml. There is little growth in the pre-pubertal period; indeed, uterine length decreases from birth to 4 years. From about 8 years of age, the uterus begins to grow, particularly the fundus. Consequently, the ratio of the antero-posterior diameter of the cervix to the fundus falls from 2:1 in infancy to 1:2 in adulthood, until menopause. Reference data pertaining to the pattern of uterine growth in adolescence have been documented and related to Tanner puberty scores. The onset of puberty is marked by an increase in the dimensions of the uterus and in endometrial thickness. The uterus changes from a tubular to a pear-shaped organ. During Tanner breast stages 1 to 5, the median uterine volume increases from 1.6 ml to 43 ml. Uterine growth continues several years after menarche and is related to the number of years after menarche but not to height, weight, or age. In women of reproductive age, mean dimensions of the uterus are: 7 cm long and 4 cm wide in nulliparous; and 8.5 cm by 5.5 cm in multiparous women. After menopause, a significant reduction in uterine size and the corpus-cervix ratio is observed. This reduction in uterine size is related to years since menopause. The decrease in size is most rapid in the first decade after menopause.

**Ovaries:** Ovaries in girls younger than 2 years of age are typically less than 1 ml in volume, although in neonates they can be slightly larger. Recent literature also documents in these young girls the presence of cysts, which are usually less than 5 mm (with the exception of neonates, where they may be larger than 1 cm). The ovaries increase in size in pre-pubertal girls with follicles up to 1 cm in size. After menarche, the ovaries are ovoid in shape and generally measure 3 x 2 x 1-2 cm. Follicles typically are present. A study of ovarian size in women of menstrual age reveals a mean ovarian volume of 10 ml. The following table lists the size and appearance of ovaries with respect to patient age.

<table>
<thead>
<tr>
<th>AGE</th>
<th>SIZE</th>
<th>APPEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>May be &gt; 1 cm</td>
<td>Follicles &lt; 1 cm</td>
</tr>
<tr>
<td>&lt;2 Years</td>
<td>&lt;1.0 cm3</td>
<td>Follicles &lt; 5 mm</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>&lt;2.5 cm3</td>
<td>Follicles &lt; 1 cm</td>
</tr>
<tr>
<td>Postpuberty</td>
<td>9.8 cm3 + 5.8 cm3</td>
<td>Follicles present</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>Decrease in size</td>
<td>Cysts seen in up to 15%.</td>
</tr>
</tbody>
</table>
FORUM: GnRH Stimulation Test

What do you feel about GnRH vs GnRH-a? (from CAPENEWS issue #12, August 2000)

Dr Usha Sriram, Chennai: I have been using 100 mcg of GnRH for testing, available as ampules for iv administration. The cost is about Rs 800-1000. The results have been good.

Dr VV Khadilkar: In Pune I am able to get GnRH with some difficulty but so far I have managed to get it when required and I follow the standard stimulation test by giving it iv in dose of 2.5 mcg/kg and then collecting samples at 0,20,60 minutes. The LHRRH has to be imported though.

Dr Vijayalakshmi Bhatia, Lucknow: I have never used agonist to test like a GnRH test, though it is mentioned in many places. The cost of the analog is also higher: the LHRRH vial costs just Rs 800 or so. For delayed puberty, I hardly ever get an LHRRH test, as it is very expensive, even when we have the LHRRH. I just do basal FSH to rule out hypergonadotrophic hypogonadism. If thinking of hypogonadotrophic hypogonadism, with age past 13 in girls or 14 in boys, I give gonadal steroid but interrupt treatment for 3 months once in about 18 months, and check the T or E2 level to rule out that spontaneous puberty has not appeared.

From CAPENEWS 6.3, December 2002: Rajesh Khadgawat wrote in October 2002: I have a few cases of hypogonadotropic hypogonadism, idiopathic type, both females and males, in whom I am planning to do the GnRH stimulation test. Is it possible to do this test with Tryptorelin 100 ugm (Inj. Decapeptyl) as I am not able to get GnRH?

Dr VL Bhatia provided a Turkish paper which answered this specifically:

Ozkan et al. A practical GnRH analog (triptorelin) stimulation test to distinguish constitutional delay of puberty (CDP) from hypogonadotropic hypogonadism (HH) in prepubertal boys. Turkish J Peds 2001: 43; 114-117.

A brief summary of the paper is as follows:

23 prepubertal boys, ages 14-16.5 years were studied. Basal blood for LH, FSH, Te was taken at 8 am, and tryptorelin (Decapeptyl) given s/c in the dose of 0.1 mg/m2. Blood for LH, FSH, Te was drawn at 4, 8 and 24 hrs. The difference in LH was most pronounced at 4 hrs: 33.2 + 9.3 vs 3.3 + 2.6 mIU/ml for CDP and HH respectively, without any overlap: range 14.1 - 44.4 vs 0.7 - 8.1. Mean incremental LH response (LH at 4 hrs - LH at 0 hrs) was significantly higher in the CDP group: 32.3 + 9.2, vs 2.6 + 2.5 in HH (range 13.7 - 43 vs 0-7). Mean LH at 8 hrs and 24 hrs were higher but overlapping. No significant difference was seen in FSH at any time point. Mean Te at 24 hrs was significantly higher in the CDP group: 369.3 ng/dl + 128.1, vs 61.4 + 22.6 in HH without overlapping (range 110 - 571 vs 21-90). Similarly, mean incremental Te response at 24 hrs was significantly higher in the CDP group, with no overlap. Mean Te at 4 hrs and 8 hrs was higher but overlapping.

The authors suggest that an LH level < 14.1 at 4 hrs, or a Te level < 110 ng/dl at 24 hrs is useful to distinguish CDP from HH.

Another good paper is summarized below:


32 prepubertal boys, ages 14 years or older, were studied; of them, 13 entered spontaneous puberty within 1 year of referral (group A), while 19 remained pre-pubertal (group B). All underwent a GnRH test (Relefact, 0.1 mg/m2 iv bolus), GnRH-a test (Decapeptyl, 0.1 mg/m2, sc), and hCG stimulation test (Chorigon 1500 units im on 3 alternate days). Basal blood for LH, FSH, Te was taken at 8 am. LH and FSH were repeated at 30 and 60 min (GnRH); or at 4 hours (GnRH-a). Te was drawn at 4 hours (GnRH-a) or on the seventh day (hCG). The LH response to GnRH-a and the Te response to hCG were significantly higher in group A than group B (LH 20.4 + 7.5 vs 2.5 + 2.0 mIU/ml; Te 18.0 + 5.9 vs 1.0 + 0.7 nmol/L), with no overlap between groups. The cut-off for the LH response to GnRH-a was 8.0 mIU/ml, and for Te to hCG 8 nmol/L. There were also significant differences between the groups in mean basal LH and FSH, and their response to GnRH, as well as Te levels 4 hr after GnRH-a, but all showed a great overlap in range.

The authors suggest that the GnRH-a and repeated injection hCG tests are reliable diagnostic tools for distinguishing CDP from HH in boys.

Given these findings, perhaps we can routinely use Decapeptyl (0.1 mg dose), which is reliably and easily available in India, for testing.
The standard gonadotropin releasing hormone (GnRH) test plays a central role in the evaluation of disorders of puberty, especially precocious puberty.

Precocious Puberty
Diagnosis

The standard GnRH test: involves administration of 100 mcg or 25-50 mcg/m2 GnRH sc or as a rapid IV bolus, with blood sampling for LH and FSH at –15, 0, 15, 30, 45, 60, 90 and 120 minutes. The average of the –15’ and 0’ values serve as the baseline LH and FSH. In menstruating females, the test should be preferably done in the early follicular phase of the cycle. Greater LH stimulation is observed if done during the luteal phase. Normally, LH peaks are generally found at 15-45'; FSH peaks may occur later in some patients. A pubertal response is defined as a marked rise in LH after stimulation, more than FSH (LH: FSH ratio >1) and indicates that the patient has a GnRH dependent or central pubertal process. After GnRH administration LH levels should at least double, and FSH rise by 1.5–2 fold. If LH and FSH fail to rise in a patient with precocious puberty, it suggests that the pubertal process in this patient is GnRH independent.

In other words, the gonadal steroid production is autonomous and not under the control of the hypothalamopituitary axis (peripheral process). The absolute increments and peak values that suggest a central vs. peripheral process should take into consideration the particular assay used, as some (ICMA, IFMA) are more sensitive than others (RIA). The best diagnostic criterion probably is a peak LH value > 9.6 mIU/mL in boys and > 6.9 mIU/mL in girls (William’s Textbook of Endocrinology, 10th edition, p1207). FSH response to GnRH test is less helpful in evaluation of pubertal disorders.

Short GnRH Test: Eckert et al (1) showed that a single LH value drawn 40’ after GnRH injected sc correlates well with the peak LH obtained after IV multiple sampling test. In their study (n=22), a discrepancy between iv and sc testing was noted only in one patient. The dose of GnRH used was the same as in the standard test, and a cut-off of 8 mIU/mL was used for diagnosis. The authors recommend this as a simple, economical test. This single sample test may be more applicable to our country where cost is a major concern. Since GnRH is expensive and not widely available, a number of alternate tests using GnRH analogs (GnRHa) have been developed for diagnosis of precocious puberty.

GnRHa Test: Different investigators have employed different analogs. The peak responses usually occur later compared to the standard GnRH test, the gonadotropins peaking at about 3-4 hours and gonadal steroids after 24 hours. Rosenfeld et al reported in 1986 that in girls with true precocious puberty, nafrelen 0.2 mcg/ kg sc gave comparable results to iv GnRH for LH and FSH at 3 hours after administration, and a far better estradiol response at 24 hours (2). Leuprolide acetate, which is more widely available, can also be used to distinguish patients with gonadotropin dependent and independent puberty (3). The protocol involves administration of leuprolide acetate 20-mcg/kg sc and measuring LH and FSH at baseline and 4hr, and testosterone/ estradiol at 4hr and 24hr. LH levels > 8-10 mIU/mL (IRMA) and an estradiol response >40pg/ml or a testosterone response >0.9 ng/ml indicates a gonadotropin dependent pubertal process.

The GnRHa test is not only easier to perform, it may be more discriminatory as it tests both gonadotrophic and gonadal steroid responses. Also GnRHa is much less expensive and more easily available than GnRH. This test therefore has a place in our practice. Its only disadvantage is the need for the patient to be available 24hr after the injection.

Monitoring therapy

Apart from the diagnosis of central precocious puberty (CPP), the GnRH test also plays a crucial role in monitoring adequacy of therapy with GnRH analogs. It has been shown that overnight monitoring of LH release is more sensitive than GnRH stimulation testing for assessing whether the dose of depot leuprolide acetate is adequate or not in children with CPP (4). However, this is expensive, impractical and not within the reach of the practicing clinician. The standard GnRH test is generally used for this purpose.
at 6 monthly intervals to confirm adequate HP axis suppression. LH levels 2hr after intramuscular depot leuprolide given as therapy, have shown good correlation with the LH peak obtained after the standard GnRH test in girls with CPP before (after the first dose) and during effective treatment (5). An LH value < 6.6 mIU/mL at 2hr indicates successful therapy. Lower values may be expected when using the chemi-luminiscence assay. This test is not only accurate but also cost effective, as only an LH level need be drawn; GnRH and multiple sampling are avoided. Probably this can be considered a reliable and convenient tool for monitoring therapy in gonadotropin-dependent precocious puberty in girls, especially on treatment with the same drug. Most studies are done in girls because CPP is more common in them. There is no reason why it cannot be equally useful in boys and our experience confirms this.

Delayed Puberty

While evaluating delayed puberty, high FSH and LH establish the diagnosis of primary hypogonadism. If gonadotropin levels are low, the possibilities are hypogonadotropic hypogonadism (HH) or constitutional delay of puberty (CDP). An LH value > 7.5 mIU/mL after GnRH suggests that the pubertal process has started, indicating CDP. If the GnRH test is negative, it has no value in differentiating these 2 conditions, since the prepubertal child with constitutional delay shows no gonadotropin response to GnRH. Again, a GnRHa test has been tried in patients being followed up for 1-5yr. Triptorelin 0.1mg/m2 given sc, with measurements of LH and FSH after 4hr and testosterone after 24hr has been validated (6) for differentiation between these two disorders in boys in one study in which the follow-up was for one year. On the other hand, DeGros et al, with a 5yr follow-up of patients after testing, showed that a single dose hCG test fares better than GnRHa for this purpose (7). Summing up, if sensitive gonadotropin assays are used, the diagnosis of PP is possible from baseline values itself. If these are not discriminatory, a short GnRH test or GnRHa test can be done as outlined above, for confirmation. Once the diagnosis is confirmed, LH can be repeated 2hr after the first treatment dose if reconfirmation of diagnosis is desired. To evaluate the adequacy of suppression on treatment, LH sample taken 2hr after injection of depot GnRHa can be repeated after the third dose.

We have been following this approach in our department, and suggest it to be ideal for our country as it is patient friendly and cost effective, while being as useful as the more expensive and time consuming tests. For delayed puberty, we recommend the single dose hCG test, if any test is to be performed, while recognizing that it may not be diagnostic for CDP versus HH and that follow-up into adulthood only will finally differentiate the two.

References

MANAGEMENT OF CONGENITAL ADRENAL HYPERPLASIA: SURGEON'S PERSPECTIVE.

Meera Luthra, Pediatric Surgeon, New Delhi, from Capenews 2005i

Congenital adrenal hyperplasia (CAH), a potentially fatal inherited disease with an incidence around 1:10,000, is caused most commonly by 21-hydroxylase deficiency (21-OHD). For purposes of brevity the rest of the discussion is confined to 21-OHD. Enzyme deficiency may be variable in severity, producing a spectrum of presentation. Affected individuals show impaired cortisol secretion and ACTH oversecretion leading to hyperplastic, androgen secreting adrenal cortices. The elevated levels of adrenal androgens in the female cause virilisation, including either clitoral enlargement or labial fusion or both to a variable degree.(1) Patients with
the virilising form of CAH are more likely to be salt losers with a more complete enzyme block (2), but the
genital changes in girls with the non salt losing form can also be severe.(3). It is sometimes difficult to be
certain when a clitoris is normal or enlarged, particularly in preterm infants and in girls with a large amount of
prepubal skin. Because of ambiguity of external genitalia, the diagnosis is often made earlier in girls; it may be
missed altogether in neonatal males presenting with dehydration and shock. Serum electrolytes usually provide
a pointer to the diagnosis, with the characteristic hyperkalemia and hyponatremia. If untreated, both sexes would
develop phallic enlargement, rapid height gain with eventual short stature, early pubic and facial hair and
muscular habitus. Boys who survive infancy would therefore present with precocious puberty. Girls may be
bought up as boys and face problems of sex reassignment.

Types of CAH

**Classical**: Salt losers and non salt losers. 66% of CAH are salt losers (4). Autosomal recessive.

**Late onset**: where the symptoms are delayed by several years.

**Cryptic**: In children of a CAH parent or relatives who are otherwise asymptomatic.

**Diagnosis**: is relatively straightforward, with high levels of serum 17 hydroxyprogesterone (17-OHP). In case of
doubt (preterm infants, sick term infants), or in older individuals, 17OHP estimation with ACTH stimulation
would provide the answer. Genetic markers are also available in several centers in Europe and the US for
confirmation of hormonal status in family members and for early prenatal diag-nosis. Later in pregnancy,
prenatal diagnosis can be made by documenting elevated levels of 17-ketosteroids and pregnanetriol in amniotic
fluid of affected fetuses.

**Treatment**

**Hormonal**: Replacement of steroids. Early institution of hydrocortisone (10-12 mg/m2) and 9a- fludrocortisone
acetate (0.15 mg/m2) is essential to control the metabolic changes. Later in childhood, prednisolone (widely
available, cheaper) may be used in place of hydro-cortisone. Adequacy of treatment is monitored with regular
assessment of height and pubertal staging, estimations of serum electrolytes and 17-OHP, and bone age. Ideally,
PRA should also be monitored, but is not easily available in India. In case of a pregnancy in which the fetus is
likely to be affected, the mother should be started on dexamethasone (which crosses the placenta) as soon as the
condition is suspected, and continued throughout pregnancy if the diagnosis is confirmed on prenatal testing (as
above).

**Surgical**: The aim is to have two separate and functional openings for the urethra and vagina. Initial techniques
practised were clitoridectomy or phalloplasty and vaginoplasty. Clitoridectomy was found unsatisfactory
because of the loss of the clitoris, which has an important sensory role. Phalloplasty was discontinued as the
erectile tissue became painful at touch or erection. Stefan (5) tried burying the phallus and obliterated the
corpus cavernosa using mattress sutures. Even this technique was not found very successful over a long period
of time. Currently the girth reduction technique (6) is most widely used since it gives the best functional and
cosmetic results, not only in children with congenital adrenal hyperplasia, but also mixed gonadal dysgenesis,
partial androgen insensitivity and exogenous androgen stimulation. The technique involves reduction in clitoral
girth rather than length, with preservation of vascular and nerve supplies, and creation of a hair pin bend in the
shaft of the clitoris, which simulates normal female anatomy as well as an apparent reduction in length; blood
loss is minimal. Since good cosmetic results can be achieved without major surgical risks, even in neonates,
most centers advocate early sex assignment and surgical correction at the earliest possible age: as soon as an
accurate diagnosis had been made, the parents had accepted the gender assignment, and the infant’s metabolic
condition had been stabilized.

**Psychological**: Due to prenatal androgen exposure, girls with CAH show variable degrees of masculinization of
the brain also. They are strongly “masculinized” in their toy and activity preferences, especially with salt-
wasting CAH, preferring boys’ toys in childhood and boy-typical activities in adolescence. They may be
masculinized/defeminized to some extent on a variety of other behaviors, including aggression, interest in
babies, and spatial ability. Parents and the child must be helped to anticipate and cope with these differences.
However, most girls with CAH also have female-typical gender identity, and marry and bear children normally,
though they do appear to have a somewhat weaker identification with females. A small percentage (higher than
the normal population) prefer lesbian relationships. It is unclear what differentiates them from other CAH
females with typical gender identity, although it looks like continuing postnatal androgenization and rearing
environment both play a role. Most centers advise early surgery, but recently, some workers are suggesting that
phallic surgery may be deferred till after puberty, when the affected individual can decide the extent and type of
correction. This is impractical yet in India, where several social taboos are attached to ambiguous genitalia.
Unfortunately, we also face a significant problem of late diagnosis, and when the girl has been brought up
initially as a boy, parents sometimes refuse later to change the gender to female. In such cases, treating physicians have little choice but to “make” the child “male”.

**Fertility:** Major factors affecting fertility in CAH are surgical creation of an adequate size vaginal introitus and non-compliance of treatment.

**REFERENCES**
PRECOCIOUS PUBERTY: DIAGNOSIS & MANAGEMENT.

PSN Menon, Armed Forces Hospital, Salamiah, Kuwait.

The age of starting puberty varies from child to child, but sexual development usually begins around the age of 11 in girls and 12-13 in boys. Appearance of primary or secondary sexual characteristics before the age of 8 years in girls and 9 years in boys is considered precocious. This disorder affects both sexes but is commoner in girls than boys. Isosexual precocious puberty indicates the appearance of phenotypically appropriate sexual characteristics whereas the term heterosexual or contrasexual indicates pubertal development inappropriate for the sex.

Common findings in girls with isosexual precocity include rapid height gain, development of breasts (thelarche), pubic and axillary hair (pubarche), and menses (menarche). In boys, deepening of voice, acne, phallic, scrotal and testicular enlargement, erections and ejaculation (spermarche) and pubic and axillary hair may be present. Children who start puberty prematurely are initially tall for age due to the growth spurt triggered by sex hormones, but because of skeletal maturation and epiphyseal closure their growth stops earlier than normal, leading to final short stature in adulthood.

Isosexual precocity is divided into 3 major types : central, peripheral and combined peripheral and central.

Central precocious puberty (CPP: also known as true or complete) is initiated by premature activation of hypothalamic - pituitary - gonadal axis through a mechanism similar to that of normal puberty, usually due to removal of normal inhibitory influences. Until recently, the majority of CPP was considered to be idiopathic. Recognized causes of CPP (Table 1) include CNS lesions (eg hypo-thalamic hamartomas, third ventricular cysts, astrocytomas and gliomas). With availability of high resolution CT and MRI scans, GnRH-secreting hypothalamic hamartomas are being diagnosed more often. The hamartomatous tissue contains GnRH neurones, which function independently of CNS inhibitory influences, like an ectopic hypothalamus episodically secreting GnRH.

Peripheral precocious puberty (PPP: precocious pseudopuberty): does not involve activation of the hypothalamic - pituitary - gonadal axis. Secondary sexual characteristics result from overactivity of the adrenals or gonads. Common causes are sex hormone producing tumors in adrenals/ ovaries/ testes, inborn enzyme errors in steroid biosynthesis causing hyperandrogenism, autonomous secretion of sex steroids, and iatrogenic/ accidental administration of sex steroids.

Combined peripheral and central precocity: Occasionally, peripheral precocity triggers off activation of the hypothalamic- pituitary - gonadal axis. The most frequent example is CPP secondary to congenital adrenal hyperplasia (CAH) or virilising tumors of the adrenal gland.

Table 1 : Etiology of Precocious Puberty

I. True/central precocious puberty
1. Idiopathic - Sporadic or familial
2. Congenital anomalies - Septo-optic dysplasia - Hydrocephalus
3. Tumors of CNS - Hypothalamic hamartoma/ LH secreting adenoma/ Optic nerve glioma/ Astrocytoma/ Ependymoma/ Germinoma/ Craniopharyngioma
4. Post-inflammaratory - Meningitis, Encephalitis
5. Post-traumatic
6. Primary hypothyroidism

II. Peripheral or pseudoprecocity
1. hCG-secreting tumors - Hepatoma/ Teratoma/ Chorioepithelioma
2. Gonadal tumors - Granulosa/ theca cell tumor of ovary/ Follicular ovarian luteal cysts/ Leydig cell tumor of testes/ Adrenal rest tumor of testes
3. Adrenal causes- Congenital adrenal hyperplasia/ Virilising adrenal neoplasm
4. Iatrogenic- Exogenous gonadotropins/ sex steroids
5. Gonadotropin-independent puberty (males)
6. McCune-Albright syndrome

**Central precocious puberty:** CPP is diagnosed if pubertal changes and laboratory findings are consistent with progressive changes of normal puberty. Most girls (five times more often than boys) and about 50% boys who develop precocity have CPP. Our experience at AIIMS has been similar, with the majority of children referred to us being girls, 80% of whom had CPP. In most girls no underlying pathology is demonstrable, unlike boys in 90% of whom the pathology can be documented.

Thelarche is the first sign of CPP in girls but growth spurt may precede or accompany breast development. Bone age is usually quite advanced. Basal and GnRH stimulated gonadotropin (Gn) levels are within the pubertal range. LH rise is greater with pubertal onset and hence is more diagnostic. Pubertal type of Gn response to GnRH is helpful in differentiating CPP from incomplete forms. In children with hypothalamic hamartomas, basal LH and FSH are often raised. Basal serum levels of estradiol/ testosterone are elevated.

If true precocity is confirmed, CT or MRI of brain with contrast enhancement should be performed. Hypothalamic hamartomas were diagnosed on MRI/ CT scans in about 25% of the children seen at AIIMS. Other tumors are rarely seen. A common recent cause of CPP is previous CNS irradiation with/ without chemotherapy, often associated with GH deficiency.

Recent development of long acting analogs of GnRH has dramatically altered the treatment of CPP, with better prognosis for final height, no serious untoward effects, and recovery of pubertal development usually within 6 months of stopping the drug.

**Peripheral precocious puberty:** in which sexual development is not under the control of an intact hypothalamic-pituitary-gonadal axis, is most often a result of CAH (commonly due to 21-hydroxylase or 11-hydroxylase deficiency) in boys. In girls, PPP is relatively rare, and results from excessive estrogen stimulation from an ovarian, adreno-cortical or exogenous source.

McCune-Albright syndrome occurs more often in girls and is characterised by osseous lesions (polycystic fibrous dysplasia) and skin lesions (cafe-au-lait spots). Other endocrine features include hyperthyroidism, hyper-adrenocorticism and pituitary gigantism. The excess hormone production appears to be autonomous.

Familial Gn-independent puberty seen in boys is characterised by autonomous Leydig cell activity. It is due to a mutation of the LH receptor, and is transmitted by fathers to their sons. The condition mimics CPP, but shows a prepubertal response on the GnRH stimulation test. GnRH analogs cannot suppress testosterone production in this disorder.

Estrogen secreting granulosa cell tumors of the ovaries are the most common neoplasms associated with pseudoprecocity in girls. Feminising adrenal tumors are rare in girls; in boys they can cause gynecomastia, virilisation or Cushing syndrome. Apart from CAH, Leydig cell tumors of testes and adrenal rests are the main causes of pseudo-precocity in boys. hCG secreting tumors producing precocity (hepatic, pineal, intracranial, retro-peritoneal and intrathoracic) are commoner in boys. GnRH agonists are not useful in these children. Treatment involves correction of the underlying cause and drugs interfering with sex steroid synthesis (testolactone or ketoconazole) or action on target cells (spironolactone).

**Combined central and peripheral precocious puberty:** is usually seen in boys with prolonged hyper-androgenism due to poorly treated CAH.

**Incomplete isosexual puberty**

Premature thelarche: is isolated breast development in girls less than 8 years of age. In most girls with this condition, breast development begins in the first year of life and in 30-40% is present at birth. The pathogenesis is probably related to estrogen secretion by the prepubertal ovary. Basal and post-GnRH serum concentrations of LH and FSH may be in the prepubertal range, though exaggerated FSH responses have been reported. Height gain is normal or increased and bone maturation relatively appropriate for chronologic age. Serum estrogen
levels may be slightly elevated and vaginal smears may show estrogentic effect. Breast development may regress and disappear (10%), regress (30%), persist unchanged (50%), or increase in size (10%).

Premature menarche: Vaginal bleeding may coour in newborn girls in the first few weeks of life because of withdrawal of maternal/placental estrogens. Vaginal bleeding of uterine origin without evidence of excessive estrogen secretion has been reported by several workers. Most of these girls have normal sexual development and regular menstrual cycles at the appropriate age with normal fertility. Linear growth, bone maturation, basal and post-GnRH stimulated Gn levels are normal for age and stage of puberty; but plasma estradiol levels are slightly elevated. Ultrasono-graphy may reveal small follicular ovarian cysts. Pathogenesis is similar to premature thelarche.

Premature adrenarche: is the increase in adrenal androgen secretion accompanying sexual maturation. The major adrenal androgens are DHEA and DHEA-S. Pubarche (appearance of pubic hair) usually occurs several years after adrenarche. Clinical signs of premature adrenarche include pubic or axillary hair growth, axillary odor and modest increase in height age relative to chronologic age. It is far more common in girls than boys, and is frequently associated with obesity and CNS insults. Bone age may be normal or advanced. Determination of serum levels of DHEA-S, or increased ratio of DHEA : 17-OHP (product : precursor ratio) may be useful in confirming the diagnosis. Differentiation from PPP may be difficult.

**DIAGNOSIS:**

In most children careful clinical history, physical examination, assessment of bone age and few hormonal measurements are sufficient for categorizing the form of sexual precocity and determining whether more extensive investigations are required. History should include exposure to exogenous hormones (Gn, estrogen, androgens), growth pattern, CNS symptoms, CNS trauma/anomalies/infections, and family history of early puberty (especially in boys). Physical examination should include pubertal staging (Tanner), height, weight, span, body proportions (upper/ lower segment ratio), body symmetry, acne, skin pigmentation, fundus and visual fields, thyroid dysfunction and neurologic evaluation. Genital examination must be done carefully (especially bimanual abdominal -rectal examination), and should include evidence of estrogenisation and clitoral size in girls, while testicular volume and symmetry and penile length and width are important in boys.

Essential laboratory investigations include x-rays for bone age (to estimate extent of stimulation and further growth potential), plasma/serum estradiol (girls) or testosterone (boys), and a GnRH stimulation test to see if Gn responses are consistent with pubertal pituitary Gn secretion (particularly LH). In menstruating girls, progesterone levels during the second half of the cycle may be done. Other hormone tests may include thyroid function tests (to rule out hypothyroidism), and plasma DHEA/DHEAS to establish whether adrenarche has occurred.

Pelvic ultrasound should be done in all girls to assess ovarian and uterine morphology and size, and appropriateness for age and stage of puberty. Ovarian cysts commonly occur in CPP as part of normal ovarian development, and in McCune-Albright syndrome. Isolated follicular cysts may present with autonomous estrogen production: these cysts are usually self-limiting and regress, with drop in estrogen level producing withdrawal bleeding. Unilateral asymmetric ovarian enlargement may suggest tumor or cysts.

All girls below 5 years and boys with CPP without any evident etiology, should have a CT/ MRI scan of CNS particularly for hypothalamo-pituitary region even if neurologic exam is normal, to rule out hypothalamic hamartoma. An EEG is generally not helpful, though EEG abnormalities are well known in CPP.

**MANAGEMENT:**

The aims of therapy are to stop or regress pubertal development and attempt to increase the final adult height. The family should be counselled and given appropriate sex education. Any underlying treatable condition should be treated appropriately, eg adrenal suppression in CAH, thyroid replacement in primary hypothyroidism, surgery, radio- or chemo-therapy in CNS, ectopic Gn-producing, gonadal and adrenal tumors. MPA, cyproterone and danazol, used earlier to induce pubertal arrest and regression, do not improve final height, but can be used if GnRH analogs are unavailable or unaffordable. Testo-lactone to block androgen action, ketoconazole to inhibit androgen production, and spironolactone have been used in combination or alone in Gn-independent precocity.

GnRH analogs abolish the natural episodic secretion of Gns by continued stimulation: this initially increases gonadotropin levels, but later causes down-regulation, returning sex steroids to prepubertal levels. GnRH analogs are available as nasal spray (Buserelin), short-acting injections (Buserelin), and depot injections.
(tryptorelin, goserelin). Treatment is monitored by clinical indices (arrest/ regression of puberty), obliter-ation of Gn response to exogenous GnRH, and in boys, fall of serum testosterone to prepubertal levels. The fall in serum estradiol in girls is not so predictable. Suppression should be confirmed 1-2 months after start of therapy, and if present, monitored at 3-6 monthly intervals. The prospects of height gain appear to be better, though long term data is scarce. After discontinuing therapy, puberty progresses normally. At AIIMS, nearly 120 children with CPP have been treated with GnRHa: mainly tryptorelin or zoladex depending on availability. 60 of these children have completed therapy and reached age 14 years. In general, good pubertal deceleration was achieved; the final adult heights were improved, but were not as satisfactory as predicted.

DRUGS FOR PRECOCIOUS PUBERTY

GnRHa:
1. Tryporelin: Decapeptyl: 3.75 mg per injection: 60-75 ug/kg/dose, on days 1,14, 28, then every 28 days. Ferring Pharma (easily available)
2. Leuprolide acetate depot: Leupron depot: 2-3 mg/kg/dose, given monthlyTAP Pharmaceuticals Inc., Denfield IL 60015, USA
3. Suprefact nasal spray: Buserlin: 1 mg/ ml: 35ug/kg/day, in 3 divided doses before meals. Behring, Hochst Actiengesellschaft, Postfact 800320, G230 Frankfurt AM, Main 80 Germany.

Others:
5. Medroxyprogesterone: Depot Provera: 150 mg per injection: 100-200 mg/ dose, given once a month; Tab Farlutal/ Prolute: 10 mg: 10-50 mg/ day in 2 divided doses.
6. Cyproterone acetate (Androcur): not available in India. 100-150 mg/m2/day in 2-3 divided doses

References


Brief abstracts of some APPES 2006 presentations (Thailand)

A pilot study of young people’s experience living with CAH in Vietnam. (Kate Armstrong, Gary Warne et al, CLAN, Australia).

A voluntary questionnaire (exploring clinic visits, acute illness management, worries, concerns, emotional supports and future hopes) was offered to young CAH patients attending Hanoi’s National Hospital of Pediatrics’ CAH support group meeting. Ten patients (10/158, 6%) responded. Most indicated a good understanding of sick day management (60%), and attended clinics annually (50%) or biannually (30%). There were no specific concerns with surgical outcomes. However, issues with body image, feelings of shame, social isolation and fear of ridicule were expressed. Emotional support came from parents and family (90%), doctors and health professionals (30%). Half the respondents identified taking medication and its high cost as a burden. Future hopes included a “normal” life, good health, a cure for CAH, and affordable access to medications.

Conclusion: This pilot study highlights the importance of family support, education, access to health care, and affordable medications for children living with CAH in resource-poor countries. Log on to www.cahclan.org
**CLIPPINGS FOR CAPENEWS**

*(aug 2006) Ram Murty Shastry, Goa*

**Novel modalities tested in the treatment of central precocious puberty (CPP)**

*a) Histrelin implant:* efficacy in suppressing gonadotropin and serum estradiol for 1 year in 11 girls with CPP is reported by Hirsch et al from Israel (Pediatrics, vol 116, no 6, Dec 2005). These girls (age at diagnosis 2-9 y, mean age 6y), previously on tryptorelin monthly im injections, had subcutaneous implants of histrelin inserted under local anaesthesia. With the implants, breast development regressed, growth velocity and bone age advancement slowed, and gonadotrophins were suppressed up to 15 months. This modality would mean less pain, less interference with work and activity, and better compliance than the standard monthly regimen.

*b) Leuprorelin 3-month depot 11.25mg* injected subcutaneously was reported by Jean-Claude Carel et al *(JCEM vol 87, no 9, 2002)* to efficiently inhibit the gonadotropic axis in 95% children with CPP studied for a 6-month period. The authors evaluated the new formulation in 44 children (40 girls) with CPP (6-month open trial). Inclusion criteria were clinical pubertal development before 8y (girls) or 10y (boys), advanced bone age, enlarged uterus >36mm, testosterone >1.7nmol/L, pubertal response of LH to GnRH (peak >5 IU/L). The principal criterion for efficacy assessment, GnRH-stimulated LH peak <3 IU/L, was met in 95% (81 of 85) of the tests performed at 3 and 6 months. Sex steroids levels also dropped significantly, and clinical pubertal development was arrested. The plasma leuprorelin levels, measured every 30 days, were essentially stable after day 60. The authors concluded that this regimen would allow reduction of number of yearly injections from 12 to 4 and thereby improve compliance.

The 3-monthly depot leuprolide is being used extensively in the US for CPP, as it is much more convenient and promotes compliance. It is available in India also. Badaru A et al *(JCEM 2006, Jan 31)* in an open 12 month trial have sequentially compared a monthly 7.5 mg dose, monthly 3.75 mg dose, and 3 monthly 11.25 mg dose of leuprolide, and found higher LH levels after the 3.75mg and 11.25 mg doses compared to the 7.5mg dose, though estrogen/ testosterone levels and clinical responses were no different. Baxter and Duffy *(Gynecol Surg 2004, Apr 17)* reported in women with endometriosis that the 3 month depot had a more detrimental effect on bone density than the monthly depot, though their period of evaluation was only 7 months. Whether various depot leuprolide doses lead to long term therapeutic differences, remains to be determined with further studies.


The authors have reported for the first time a family with familial male-limited precocious puberty (FMPP) due to D564G mutation of the LHCGR (luteinizing hormone/ choriogonadotro-pin receptor) gene, wherein the family showed a varied phenotypic expression (severe precocity unresponsive to therapy with compromise of the predicted final height in some members, to attainment of tall final stature in others who never received medical treatment). DNA amplification and sequencing of exon 11 of the LHCGR gene was done for the affected members and their mother, which showed an A → G nucleotide substitution at position 1691 leading to an aspartic acid to glycine substitution in the receptor at amino acid 564.

The index case presented with precocious puberty at 4½ yrs. His height was 122.9 cm (1.9 SD above the mean for age), bone age 10 yr, predicted adult height 163 cm while his mid-parental height was 182 cm. His testes were 6 cc in volume. His serum testosterone level was 254 ng/dl, while gonadotropin and HCG levels were undetectable. GnRH/ LHRH stimulation test revealed a prepubertal response. High dose ACTH-stimulation test was normal, ruling out congenital adrenal hyperplasia.

The index case has 2 maternal half-brothers with precocious puberty. One of the half-brothers, 14 yr old and 187.9 cm, began puberty between 4-5 yr. The other halfbrother, 17 yr and 180.3 cm, had obvious signs of puberty at 2½ yrs of age. The midparental height for the half-brothers was 184 cm and both had bone ages of 18 yr. The index case’s maternal grandfather had pubertal onset before the age of 5 and achieved a final adult height of 162.5 cm, which was unusually short for his family. This man’s brother, who reportedly did not have precocity and achieved final stature of 185.4 cm, had a son with precocious puberty and short stature. The index case’s maternal grandfather also had a son who had puberty at 2 yr and is said to be tall.
The index case was put on testolactone and spironolactone, which was later replaced by flutamide. Lupron DEPOTPED was added at 6 yr after a GnRH stimulation test showed central activation of puberty. The index case continued to experience rapid growth and sexual maturation despite therapy.

This report puts forth the possibility that the effect of mutant LHCGR gene, D564G, on phenotypic expression of FMPP, such as final adult height, is modified by other genetic factors. Thus, more studies are needed to correlate genotype with phenotype.
Delayed puberty, chronic illness:
In a retrospective analysis of causes of pubertal delay in an endocrine clinic in north India, chronic systemic illnesses like malnutrition and tuberculosis were found to be the largest group (40%), followed by hypothyroidism (20%). Since these are potentially treatable causes, care should be taken to recognize them early. (BK Bhakri, K Biswas)

Screening first degree relatives of PCOS patients:
191 first degree relatives of 99 PCOS patients were evaluated and compared against matched controls. They were found to have a higher prevalence of diabetes, IGT, metabolic syndrome, and HOMA-IR. BMI and waist hip ratio were found to be strong predictors of IR. (P Kalra, E Bhatia)

DSD: Strategies for surgical intervention in DSD:
Major changes in practice were reiterated: children with minor degrees of clitoral enlargement are less likely to be offered clitoral reduction than they once would have been. Families should be offered the option of deferring reconstructive surgery for their child with ambiguous genitalia. Truthful disclosure makes it possible to have a free and open discussion about the facts with the patient as well as the parents. (G Warne)

Long term outcome studies in congenital adrenal hyperplasia:
Women with salt wasting forms of CAH have more pain and discomfort during intercourse, are overall less sexually active, and experience a range of emotional disorders, including gender dysphoria. Men with poorly controlled CAH have a high incidence of adrenal rests in their testes; these obstruct the hilum, causing infertility. These adrenal rests may also be mistaken for cancer and testes may be unnecessarily removed. (G Warne)

Genetic analysis of SRD5A2 (5 alpha reductase enzyme gene):
The known missense mutation pR246Q in exon 5 of SRD5A2 was found in 2 patients with 5 alpha reductase enzyme deficiency. PCR RFLP could be used for a quick provisional diagnosis of this mutation where clinically compatible. (E Bhatia)

Cushings disease:
A retrospective analysis of 44 cases of pediatric Cushing’s disease has shown comparable sensitivity of clinical features in making a diagnosis as a combination of dynamic tests and imaging modalities. It was interesting to note that of the 4 patients who had to undergo bilateral adrenalectomy, 3 developed Nelson’s syndrome within a short average duration of 5 months. (N Shah)

Cushing’s disease and growth:
*** Growth retardation is a hallmark of Cushing’s disease; associated with reduction in mean 24 hour levels of GH and the amplitude of its secretory pulses. Hypercortisolemia suppresses the amplitude of GHRH pulses while increasing that of somatostatin. A direct pituitary action may also be present.*** GH hyposecretion may persist for 1-9 years after remission of Cushing’s disease. This results in lack of catch-up growth in these patients.
*** Direct adverse effects are seen on the growth plate also. Expression of the GH receptor is downregulated in chondrocytes, resulting in reduction of local IGF- 1 production. Hence, a GH resistant state occurs and this persists after remission.
*** Impact of glucocorticoids on bone mineral density, with resultant osteoporotic fractures especially involving trabecular bone, may be an additional reason for poor linear growth. Close monitoring of growth after documenting cure is necessary for timely intervention. GH±GnRH therapy is indicated at the earliest. (N Shah)