

IDIOPATHIC PRECOCIOUS PUBARCHE (IPP): ALWAYS A "PHYSIOLOGIC VARIATION" OF NORMAL PUBERTY?

V. L. Brunelli¹, A. Vitaliti¹, C. Franzoni¹, A. Farolfi¹, M. Fontana¹

¹Department of Pediatrics, Children Hospital, Vittore Buzzi, ICP, Milano

BACKGROUND

- Idiopathic precocious pubarche (IPP) in girls can be a sign of future adult diseases. IPP can precede polycystic ovary syndrome (PCOS) (L. Ibanez, 1993) or functional ovarian hyperandrogenism (RJ Teixeira, 2001). These risks are high in low birth-weight girls, in which adrenal hyper function and insulin resistance are strategies in achieving catch-up growth (L. Ibanez, 1998).
- Adrenarche is usually associated with pubarche and other mild clinical features of androgen activity, as acne or body odour, but adrenarche and pubarche are not the same. In girls, adrenarche seems to be a necessary but not sufficient condition for pubarche. MR Palmert (2001) and DD Martin (2004) hypothesized a role of ovarian steroids and links between adrenal and ovarian activities. Nevertheless it is well known that adrenarche and gonadarche are separated events (PA Lee, 1976; L. Iughetti, 2005).
- Seldom, in females, physiologic puberty can start with pubarche instead of telarche.
- We observed that in some cases, IPP can precede a slow progressive precocious puberty in girls.

AIMS

- To examine differences in clinical presentation and/or in plasma hormonal profile, between subjects with a simple IPP and subjects with IPP, followed by anticipated puberty.
- To verify if the IPP subjects with anticipated puberty are the same subjects at risk of hyperandrogenism and hyperinsulinemia in adulthood.

SUBJECTS AND METHODS

- We studied 20 girls with IPP, mean age 4,7 years (age range 4 - 7,5), followed during years 2001-2005.
- All patients underwent clinic evaluation, radiological study of the left wrist for bone maturation and plasma hormonal profile. This consisted in measures of: cortisol, DHEAS, Androstenedione, Testosterone, Estradiol, 17OH-progesterone, at basal condition and after one hour from ACTH (0.1 mg ev) stimulation.
- In selected cases, sonography of adrenals and/or pelvis was performed. Two subjects with late onset 21-hydroxylase deficiency, detected by hormonal, genetic and molecular investigations, were excluded from the study. The remaining 18 out of 20 subjects were divided in:
 - group A: 12 girls with simple precocious idiopathic pubarche;
 - group B: 6 girls with IPP, developing slowly progressive precocious puberty.
- Precocious puberty was diagnosed when telarche appeared below 8 years of age and plasma LH and FSH levels after LHRH raised in pubertal range.

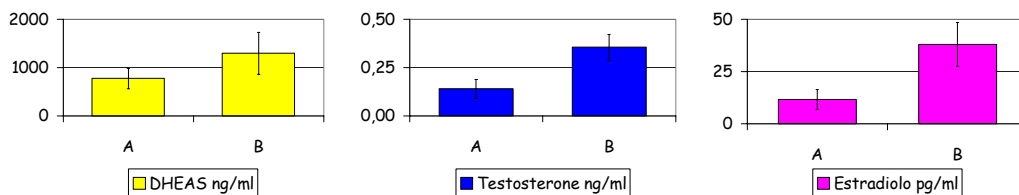
RESULTS

- **Familiar data:** No difference was detected in mid parental height between groups. Mean age of maternal menarche was not significantly different too. Clear familiarity of PCOS was not evident in any case.
- **Clinic:** 2 subjects (16%) were small for gestational age (SGA) in Group A; 3 (50%) in Group B. All patients had a height between +1,5 and +2 z-score for age. In both groups growth velocity was not significantly advanced. No over-weight or obesity were present. Bone age was advanced (+1,5 SDS) in all girls, without differences between groups.
- **Hormonal Data:** In Group B mean DHEAs, testosterone and estradiol basal plasma levels were higher than expected for age and significantly higher than Group A (see table 1 and figure 1). Between the two groups, no overlapping values were present in testosterone and estradiol dosage. Other basal and stimulated adrenal and gonadal steroids were not different between groups. In particular no difference was evident in 17OHP at 60' after ACTH stimulation. Moreover, in both groups A and B, mean 60' 17OHP level was in the range of 21hydroxylase-deficiency heterozygotes: 3.27 + 1,18 and 3.45 + 2, respectively.

Table 1

groups	DHEAS ng/ml (mean ± SD)	Testosterone ng/ml (mean ± SD)	Estradiol ng/ml (mean ± SD)
A	774 ± 422	0,2 ± 0,09	11,7 ± 9
B	1294 ± 866	0,5 ± 0,13	38 ± 20
	p < 0,05	p < 0,0025	p < 0,006

Figure 1



QUESTIONS and DISCUSSION

Our preliminary and very incomplete data suggest that IPP subjects, prone to develop a true precocious puberty, often have low birth-weight. They show a significant rising in basal testosterone and estradiol plasma levels, since the first stage of their pubertal development.

Why true pubertal precocity is present only in some IPP subjects?

In most cases, elevation of adrenal androgens, have poor effect on pubertal development (L. Ibanez, 1992) but in others it may trigger the activation of puberty (untreated congenital adrenal hyperplasia). Among girls with IPP, some could produce a larger amount of adrenal androgens: SGA, 21OH-deficiency heterozygotes, certain obese.

On the other hand, pubarche followed by true anticipated puberty, could be the first sign of an anticipated ovarian activity in subjects with an increased androgen receptor sensitivity. Old studies have yet correlate androgen receptor gene CAG-repeat polymorphism with androgen receptor activity (A Edwards, 1992). Recent data have correlate this polymorphism with precocious pubarche (L. Ibanez, 2003).

In other words, precocious pubarche can be the final result of different and alternative links among adrenal, ovary, central nervous and genetic ground.

Are IPP with successive anticipated puberty, a subpopulation among subjects at risk of adult metabolic disorders (PCOS, ovarian hyperandrogenia, hyperinsulinemia, altered body composition etc)? Which the role of genetic and environmental factors?

Our data can be the starting point for a larger observation of pubertal progression in subjects with IP.

Proposta studio pubarca precoce

PREMESSA

- Molti dati sono stati pubblicati per cercare di comprendere se il pubarca precoce isolato sia un fenomeno parafisiologico oppure possa essere il primo segno, in età pediatrica, di disturbi metabolici ed ormonali in età adulta: iperandrogenismo ovarico, resistenza insulinica, sindrome dell'ovaio policistico (L Ibanez, 1993; RJ Teixeira, 2001). Il follow-up di queste bambine non è così lungo da avere una reale verifica. In ragazze con storia di pubarca precoce è stata segnalata una maggior frequenza di irregolarità mestruali, acne e ed irsutismo. Alcune caratteristiche metaboliche (iperinsulinismo) e di massa corporea (maggiore massa grassa rispetto ai controlli, grasso a disposizione centrale) simili a donne adulte con PCO sono state trovate anche in bambine con pubarca precoce. Queste caratteristiche sembrano essere più frequenti nei soggetti con pubarca precoce, con storia di 'basso peso alla nascita' e buon 'catch-up growth' (L Ibanez, 1998).
- Il segno clinico 'pubarca' benchè associato ad adrenarca non coincide con esso. Recentemente è stato ipotizzato un ruolo anche degli androgeni ovarici (MR Palmert (2001), DD Martin 2004). Da anni, tuttavia gonadarca ed adrenarca sono ritenuti fenomeni indipendenti. (PA Lee, 1976; L Iughetti, 2005).
- Anche la pubertà fisiologica può esordire, in un limitato numero di casi, con pubarca invece di telarca. Personalmente ho osservato che 6 bambine su 18 con pubarca precoce hanno sviluppato una vera pubertà anticipata.

SCOPO

- Verificare la reale incidenza di pubertà anticipata in una popolazione di bambine con pubarca precoce.
- Verificare eventuali differenze cliniche, auxologiche e di assetto metabolico-ormonale tra bambine con pubarca precoce semplice e bambine con vero anticipo puberale esordito con pubarca.
- Verificare se le bambine con anticipo puberale corrispondono a quei soggetti a rischio di iperandrogenismo ed iperinsulinismo anche in età adulta..

CASI, ESAMI DI CONTROLLO-

- Reclutare 100 o più casi di bambine con pubarca precoce idiopatico.
- Anamnesi familiare per: ipertensione, diabete, età menarca materno, irregolarità mestruali, PCOS, distiroidismi.
- Anamnesi personale: peso, lunghezza alla nascita,, abitudini alimentari, attività sportiva
- Controlli clinici semestrali per: crescita, valutazione di progressione puberale.
- Controlli radiologici semestrali per: maturazione scheletrica,
- Ecografia pelvica annuale con calcolo volume ovarico, valutazione morfologica utero e ovaie.
- Valutazione ormonale all' ingresso:
 - ACTH test,
 - glicemia, insulinemia basali, lipidogramma, OGTT?
 - estradiolo, TSH, fT4.
 - LHRHa test
- Ripetizione di esami ormonali nel follow-up, su indicazione clinica.