# NON CLASSIC 21 HYDROXYLASE DEFICIENT ADRENAL HYPERPLASIA IN PATIENTS WITH ISOLATED PRECOCIOUS PUBARCHE

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**Abstract-** Precocious Pubarche (PP) is most often a benign condition secondary to the early appearance of adrenarche. However, PP may be a manifestation of mild errors of steroidogenesis in particular non classic 21 hydroxylase deficiency (NC210HD). The incidence of NC210HD in patients with PP ranges from about 0-30% of cases in various reports. Controversy exists as to whether all children with PP should undergo an ACTH test. This study was designed in order to determine 1) the frequency of NC210HD in children with isolated PP 2) to determine whether basal 17 hydroxyprogestrone (17OHP) values could help distinguish patients who are at risk for having NC210HD and thus should have an ACTH test. We studied 54 subjects (38 girls and 16 boys) aged 6.5±1.4 yr with isolated PP. Twenty five normal subjects (10 age matched and 15 pubertal) were studied as controls. Blood samples were drawn at baseline for dehydro-epiandrosterone (DHEA), androstendione (A), and 17α-hydroxy progesterone (17OHP). An ACTH stimulation test (synacthen 0.25 mg IV bolus) was performed and 1 hr post injection 17OHP was evaluated. Bone age was determined in all subjects. Using published normogram standards for the serum 17OHP response to ACTH, 3 patients (5.5%) were diagnosed as having NC210HD. In all patients diagnosed as having NC210HD, basal 170HP level was higher than pubertal value. Thus, from a clinical point of view, the ACTH test in patients with typical pubarche must be reserved for subjects with high basal 170HP levels.

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**Key Words:** Precocious Pubarche, Non classic 21 hydroxylase deficient adrenal hyperplasia (NC210HD), ACTH test

## INTRODUCTION

Precocious pubarche (PP) is characterized by the appearance of sexual hair before the age of 8 yr in girls or 9 yr in boys without other evidence of secondary sexual maturation. PP is most often a benign condition (1,2), usually followed by a normal timed true puberty (3). This benign form is secondary to the early appearance of the adrenarche and is, therefore, also called precocious adrenarche (PA). The underlying mechanism of PA appears to be early maturation of the zona reticularis of the adrenal cortex, independent or partially dependent on ACTH, resulting in increased production of adrenal androgens in particular 5-ene androgens (DHEA) (1-4). Postnatally, non classic 21 hydroxylase deficiency (NC210HD) can produce any array of hyperandrogenic symptoms including PP, advanced bone age and accelerated growth in childhood (1-2). The peri or postpubertal onset of hyperandrogenism in females secondary to adrenal 21-OH deficiency was initially reported by Jayle and Colleagues in 1958 (5). Epidemiologic and molecular genetic studies have shown that the prevalence of NC210HD is about 0% (6) to 30% (7) of unselected children presenting with PP. This discrepancy may be due to several factors. NC210HD is in fact extremely common, occurring in approximately 0.3% of the general white population, 1.6% of Yugoslavs, 1.9% of Hispanics and 3.7% of Ashkenazi's Jews (8). The ACTH stimulation test is considered to be necessary to differentiate NC210HD from PP (9-14). Same researchers suggest that an ACTH test should be performed only in patients with associated one or more features of systemic androgen effect such as marked growth acceleration, clitoral (girls) or phallic (boys) enlargement, cystic acnea and advanced bone age (>2 SD above the mean for age) (2-3). The aim of this study was 1) to determine the frequency of NC210HD in patients presenting with isolated PP 2) to determine whether basal 170HP level help to distinguish which patients needs to ACTH stimulation test.

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## MATERIALS AND METHODS

### Subjects

Fifty four subjects (38 girls and 16 boys) aged 6.5±1.4 yr (range, 1-8 yr) with PP who had been observed over the past 8 yr were evaluated. All

patients were examined by pediatrics endocrinologist at the time of presentation and all patients presented pubic hair stages II-III according to the classification of Marshall and Tanner. None of the children had signs of systemic virilization (eg. increased muscle mass, clitoromegaly or phallic enlargement). None of the males had testicular size greater than 2.5 ml. None of the females had breast development. Blood pressure was normal in all subjects. Control subjects included 10 age matched normal children (6 girls and 4 boys). To avoid overdiagnosis of steroidogenic defect, 15 pubertal normal children (10 girls and 5 boys) with Tanner stage II-III pubic hair were also evaluated.

### Methods

An ACTH stimulation test (synacthen, 0.25 mg IV bolus) was performed in all subjects at 8 AM. Blood samples were drawn at base line for dehydroepi androsterone (DHEA), androstendione (A), and 17α-hydroxylase progestrone (17OHP) and 1 hr postinjection 17OHP was evaluated in all subjects. DHEA, A and 170HP were measured by RIA. Bone age was determined by comparison to the standard of Greulish and Pyle.

### Biochemical definition of NC210HD

The diagnosis of NC210HD was made using a published normogram standard for the serum 170HP response to ACTH (10). On the basis of these criteria, when no enzyme defect was found, the patients were classified as having precocious adrenarche (PA).

### Statistical analysis

All results are presented as the mean±SD. Differences between groups means were determined by analysis of varience followed by student's t-test. $P<0.05$ was considered statistically significant.

## RESULTS

### Hormonal data

Basal values of steroids in children with PP and in normal prepubertal (PPC) and normal pubertal (PC) subjects are reported in table 1. The 170HP response to ACTH are reported in table 2. Our normal control values did not differ from previously reported levels (3). As there was no difference between the results obtained in females and males with PP, the hormone values were pooled in to one group.

**Table 1.** Basal steroid values

| steroid | controls | | PP | |
|---|---|---|---|---|
| | **Prepubertal (6F, 4M)** | **Pubertal (10F, 5M)** | **PA (35F, 16M)** | NC210HD (3F) |
| 17 OHP (ng/dl) | **36.3±19.8 (26.4-46.2; n=10** | **56.1±23.1 (46.2-66; n=15)** | **46.2±29.7 (9.9-165; n=51)** | 381.7±114.6 (265-494; n=3) |
| DHEA (ng/dl) | **54.7±37.4 (37.4-74.9; n=10)** | **244.9±74.9 (210.3-276.6; n=15)** | **219±115.2 (23-574.5; n=51)** | 463.9±144 (288.1-622.4; n=3) |
| A (ng/dl) | **22.9±11.46** (17.1-28.6; n=10) | **100.2±34.3** (83-114.6; n=15) | **68.7±45.8** (11.4-214.8; n=51) | 143.2±77.3 (63-257.8; n=3) |

Values are the mean±SD, the range and number of subjects are in the parentheses. 170HP, 17 hydroxyprogestroe; DHEA, dehydroepiandrosterone; A, androstendione.

**Table 2.** Values of 170HP before and after ACTH stimulation

| 17OHP (ng/dl) | controls | | PP | |
|---|---|---|---|---|
| | **Prepubertal (6F, 4M)** | **Pubertal (10F, 5M)** | **PA (35F, 16M)** | NC210HD (3F) |
| Basal | **36.3±19.8 (26.4-46.2; n=10)** | **56.1±23.1 (46.2-66; n=15)** | **46.2±29.7 (9.9-165; n=51)** | 381.7±114.6 (265-464; n=3) |
| After ACTH | **155.1±52.7** (125.4-181.5; n=10) | **161.7±92.4** (118.8-204.9; n=15) | **135.3±59.4** (29.7-280.5; n=51) | 1942.7±691 (1274-2650; n=3) |

Values are the mean±SD, the range and number of subjects are in the parantheses.

**Table 3.** Nonclassical 210HD adrenal hyperplasia in patients with PP

| Authors | **Subjects** | **NC210HD** |
|---|---|---|
| Morris et al (6) | **28F, 3M** | 0 |
| Temeck et al (7) | **19F, 4M** | 6F, 1M (30%, 3A, 3H, 1IT) |
| Hawkins et al (9) | **46F** | 3 (6.5%) |
| Rappaport et al (15) | **30F, 3M** | 2F (6%) |
| Oberfield et al (16) | **32F, 2M** | 0 |
| Siegel et al (17) | **47F, 11M** | 5F, 1M (10%) |
| **This report** | 38F, 16M | 3F (5.5%) |

A, Ashkenazi; H, Hispanic; IT, Italian

### Subjects with PA

Fifty one subjects (35 girls and 16 boys) with no enzyme defect were diagnosed as having PA.

In these patients basal and stimulated 170HP levels were significantly lower than those in NC210HD subjects ($p<0.001$), no differences were found vs. the other groups. Basal plasma DHEA levels were significantly higher than PPC values ($p<0.001$) and significantly lower than NC210HD ($p<0.001$).

Basal plasma A levels were significantly higher ($p<0.001$) than PPC and significantly lower than NC210HD ($p<0.001$).

### Subjects with NC210HD

Three patients of 54 (5.5%) were diagnosed as having NC210HD using the published normogram standard (10). All of the 3 patients were female. In these patients, both basal and stimulated plasma 170HP levels were significantly higher than in all groups ($p<0.001$). Basal plasma A levels were significantly higher than values in the PA, PPC ($p<0.001$) and PC groups ($p<0.005$).

## DISCUSSION

The aims of this study were: 1) to dertermine the frequency of NC210HD in patients with isolated PP 2) to dertermine whether basal 170HP level could differentiate patients who required an ACTH test. Until now the true incidence of NC21OHD has not been established, so it is not clear whether an ACTH test should be included in the diagnostic procedures in patients with precocious pubarche. Numerous studies have reported evidence of non classical adrenal hyperplasia in precocious pubarche and the incidence of NC210HD reported in literature ranges from about 0% (6) to 30% of cases (7) (Table 3). This large discrepancy depends on several factors: ethnic origin, number of subjects studied and differences in patient selection criteria. As far as the first aim of our study is concerned, 3 patients out of 54 (5.5%) were diagnosed as having NC210HD on the basis of the published normogram standard for the serum 170HP response to ACTH. Basal hormonal levels were helpful in detecting NC210HD, as 170HP levels were higher (>2 SD for pubertal controls) without overlap with the values of other groups. In these cases, an ACTH stimulation test must be performed to confirm the diagnosis. Fifty one out of 54 patients with no biochemical evidence of an adrenal biosynthetic defect were diagnosed as having isolated precocious adrenarche (PA). In agreement with previous results (11), these subjects show adrenal androgen levels higher than those in normal prepubertal children and comparable with Tanner stage 2 of pubic hair development. In sumarry, NC210HD is present in 5.5% of patients with isolated PP in this study that is compatible with Rappaport et al. report (15). In agreement with previous results (6,9,15), in these cases basal plasma 170HP levels are often already diagnostic, in that they are always higher than pubertal control values. Thus, from a clinical point of view, the ACTH test in patients with typical pubarche must be reserved for subjects with high basal plasma 170HP levels to diagnose NC210HD, wheras in subjects with normal basal 170HP levels, a close clinical observation may be the initial pereferable management option.

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