E-ISSN : 2963-4946
Vol. 1 No. 11 August 2023
Asian Journal of Social and Humanities
https://ajosh.org/

Peripheral Precocious Puberty In A Four Years Old Boy With Classic Simple Virilizing Congenital Adrenal Hyperplasia

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KEYWORDS
Precocious Puberty, Classic Simple Virilizing, Congenital Adrenal Hyperplasia

ABSTRACT
The study aims to describe a case of precocious puberty caused by classic simple virilizing congenital adrenal hyperplasia. This is a case of 4 years-old boy who developed premature pubarche 5 month before consultation. Patient also has penis enlargement with prepubertal testes and facial acne since age of three. His voice also changed to be more like an adult male voice. Physical examination revealed an alert boy, with normal vital sign, body weight of 27 kilograms (>P95, CDC Growth Chart 2000) and height of 126 centimeter (>P95, CDC Growth Chart 2000), with advanced bone age of 14-years-old child. The Sexual Maturity Rating score was G1P3(tanner stage 3), and his height was more than his mid-parenteral height. Laboratory test was done revealed 17-OHP of 196.03 ng/ml (n: <= 0.90ng/ml), high level of testosterone at 270.1 ng/ml (n: <= 0.19ng/ml), level of B-HCG : <2.3mIU/ml, low level of LH : 0.1 mIU/ml (n: >0.6 mIU/ml), and low level of FSH: 0.1 mIU/ml (n: 0-5.0mIU/ml). Ultrasound of Kidney shows a picture of hyperplasia of left adrenal gland. All of these findings allowed diagnosing him with classic simple virilizing congenital adrenal hyperplasia. Based on this diagnosis, he was then started on hydrocortisone, and after 6 months of starting the treatment, he has a favourable clinical outcome, without any secondary sex characteristics or bone age progression. Peripheral precocious puberty due to classic simple virilizing congenital adrenal hyperplasia may be asymptomatic from birth to the preschool age, therefore early detection, immediate and appropriate managements are crucial and important to prevent late outcomes.

Introduction

Precocious puberty is defined as the appearance of signs of puberty before the age of eight in girls and age of nine in boys. Its estimated incidence is 1:5000–1:10.000 (both sexes). It presents symptoms and requires swift diagnosis to prevent adverse effects on the child's growth, development and future physical and mental health. Precocious

puberty may be divided into central precocious puberty and peripheral precocious puberty (PPP). Peripheral precocious puberty results from peripheral production of sex steroids, independent of activation of the hypothalamic pituitary gonadal axis. It is much less common than central precocious puberty (De Leon et al., 2021). Causes are variable and can be congenital or acquired, such as in congenital adrenal hyperplasia (CAH), McCune Albright syndrome (MAS), Familial male-limited precocious puberty (FMPP), and sex steroid secreting tumors. The most common causes of PPP is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency resulting in excess androgen production (Sumińska et al., 2020). Males with 21-hydroxylase deficiency, in the absence of salt wasting, often present at a later age with precocious puberty, and it happens 10-15 fold lower than girls making PPP in boys is less common than in girls (Merke, 2013). In Asia countries, for example in Saudi Arabia the incidence of PPP in boys is less than 1% of the population (Pulungan et al., 2020).

Males with the classic non-salt-losing form tend to have an early growth spurt, but their final adult height is usually shorter than others in their family, and if the patient is not identified by neonatal screening, symptoms usually present at two to four years of age till preschool age with early virilization and mostly come with manifestation of precocious puberty, that caused by excess of androgen hormone (Rodríguez et al., 2017). These less-severe forms of disease have onset in childhood and are characterized by signs of virilization: premature pubarche, normal genitalia, accelerated growth and bone maturation, hirsutism, severe acne and with no evidence of aldosterone deficiency so they do not experience salt loss. The goals of treatment are replacing the physiological secretion of glucocorticoids and controlling manifestations associated with hyperandrogenism while avoiding overtreatment and improving adult outcomes. Another goal is to treat patients with the minimum effective dose so they can remain asymptomatic, have a normal growth and pubertal development.

Research Methods

IKAA, 4 years-old boy was reffered from BM Private Hospital in one of district area in Bali with chief complaint of growth of pubic hair since 5 month prior consultation. Hair growth was not found elsewhere. Patient was also noted to have penis enlargement with prepubertal testes and facial acne since age of 3 years. His voice also changed to be more like an adult male voice. Patient was born from healthy and non-consanguineous parents, gestation of 39-40 weeks, delivery via C-section, due to breech position. Weight and height of birth was 2700 grams and 50 cm, respectively. He was born vigorously and there was no history of respiratory distress. He was sent home 2 days after delivery. Patient was active and had good relationships with other peer groups. There was no history of repeated vomiting, dehydration or extreme muscle weakness. Family history of ambiguous genitalia was denied. There was no history of hormonal therapy and genetic abnormalities in the family (Merke & Raby, n.d.).

Physical examination revealed an alert boy, who looked very active. The pulse rate was 92 times per minute and regular, respiratory rate was 22 times per minute, axillary temperature was 36.8°C, blood pressure was 90/60 mmHg. His body weight was 27 kilograms (>P95, CDC Growth Chart 2000) with body height was 126 centimeter (>P95, CDC Growth Chart 2000) . Head circumference was 53 centimeter (between 1 and 2 SD). The height of upper segment (US) and lower segment (LS), were 67 centimeter and 69 centimeter respectively, with ratio US/LS was 0.97 . The length of arm span was 130 centimeter. Her mother’s height was 145 centimeter, meanwhile her father’s height

was 176 centimeter. His mid-parental height was 167 centimeter tall with the range of potential genetic was 158.5-175.5 centimeter. The hair was fine and black. No dysmorphic picture. The conjunctivas were not anemic or icteric, with normal pupil reflexes. Mustache had not grown yet. No hyperpigmentation of the skin was noted. The chest examination revealed normal chest shape, no visible deformities, there were no thrill nor heave. On auscultation, the first and second heart sounds were normal, without murmur. The movement of both sides of the chest was symmetrical. Vesicular respiratory sounds was noted, without wheezing or rales. The abdomen was not distended with normal bowel sounds and no hepatosplenomegaly. Prader staging and virilization of genitalia eksterna was stage V with a normally formed penis with the urethral opening at the tip and prepubertas testes , the length of the phallus is about 6 cm (stretched length from pubic tubercle to tip of penis), genitalia externa was virilitation with pubic hair as

shown in figure 1 . Tanner Stage of the patient was : Tanner Stage III , G1P3.

Figure 1 : genitalia externa was virilitation with pubic hair and enlarge of the penis size for a 4 years boy

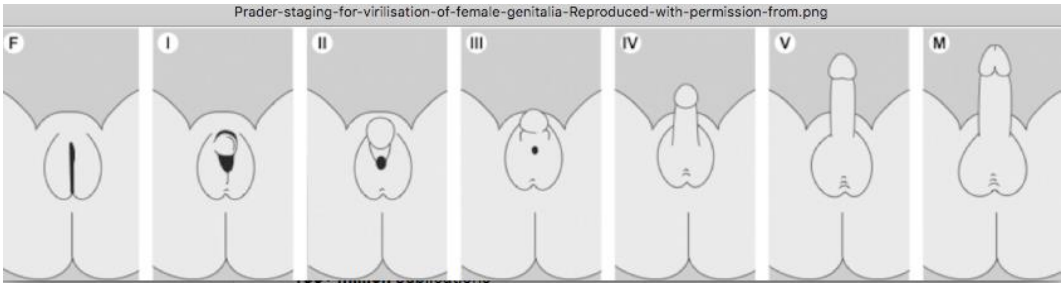

Figure 2 : Prader staging and virilization of genitalia external

Laboratory tests were done revealed 17-OHP of 196.03 ng/ml (n: <= 0.90ng/ml), high level of testosterone at 270.1 ng/ml (n: <= 0.19ng/ml), level of B-HCG : <2.3mIU/ml, low level of LH : 0.1 mIU/ml (n: >0.6 mIU/ml), and low level of FSH: 0.1 mIU/ml (n: 0-5.0mIU/ml). Serum sodium and potassium were normal with value of 138

and 3.7 respectively. At age 4 years old, his bone age was equal to that of 14 years old male. Upper abdomen ultrasound revealed a picture of hyperplasia of left adrenal gland.

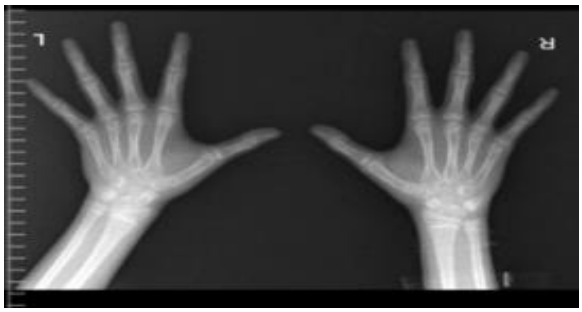

Figure 3 : Bone Age is equal with bone age of 14 years old of boy (early and mid puberty)

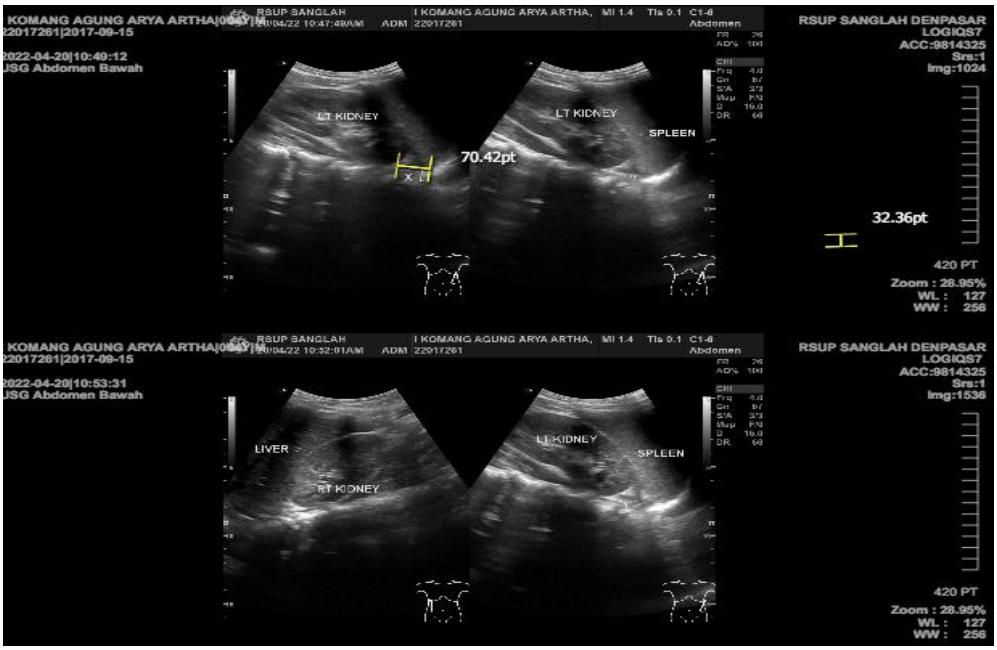

Figure 4 : Upper abdomen ultrasound revealed a picture of hyperplasia of left adrenal gland

Based on the clinical manifestations, laboratory findings, and radiology imaging, patient was then diagnosed with peripheral precocious puberty et causa classic simple virilizing CAH. Treatment was started using hydrocortisone , a glucocorticoid , at dose of 10 mg/m2, at outpatient basis and being followed up regularly every month in pediatric endocrinology clinic, at Prof Ngoerah General Hospital (Sperling, 2021).

Results and Discussions

Precocious puberty is an early onset of puberty and early onset of secondary sexual characteristics in children. It is a very challenging diagnosis as the differential diagnosis varies from benign variants to serious conditions. Precocious puberty classifies into two major categories based on the etiology: central precocious puberty and peripheral precocious puberty. One of the etiologies of peripheral precocious puberty is congenital adrenal hyperplasia (CAH). CAH refers to a group of genetic disorders that affect the

adrenal glands, a pair of walnut-sized organ above the kidneys (White & Speiser, 2000). The adrenal glands produces important hormones including cortisol, mineralocorticoids and adrogens. In Indonesia, one in 594 screened babies, is found to have CAH. Simple virilizing (SV) CAH is the moderate form of classic 21-hydroxylase deficiency. Simple virilizing CAH involves no aldosterone deficiency. Therefore, there are no severe or life-threatening sodium-deficiency symptoms in patient and is usually ignored in boys because excess of androgen during childhood results in overgrowth and early signs of puberty.

The main difference between the salt wasting and simple virilizing - CAH forms is the insufficient aldosterone secretion in salt wasting type that leads to a fatal drop of electrolytes in the first. The normal electrolyte levels observed in SV-CAH might be explained by the role of testosterone as a down-regulator of aldosterone secretion. Unfortunately, we were not able to measure the aldosterone level in our patient, because the test is not available in Indonesia. In our case, our patient was referred due to early puberty signs. The patient came due to growth of pubic hair since 5 month before consultation with penis enlargement and prepubertal testes. Patient also had facial acne since age of 3 years , his voice also changed to be more like an adult male voice. He was diagnosed with 21-hydroxylase deficiency based on a 17-OHprogesterone level of 196.03 ng/ml. Prader staging and virilization of genitalia eksterna is stage V with a normally formed penis with the urethral opening at the tip and prepubertal testes, the length of the phallus is about 6 cm (stretched length from pubic tubercle to tip of penis), genitalia externa was virilitation with pubic hair. His bone age was equal to that of 14 years old male. Upper abdomen ultrasound revealed a picture of hyperplasia of left adrenal gland.

Based on the clinical manifestations, laboratory findings, and radiology imaging, patient was then diagnosed with Peripheral Precocious Puberty with classic simple virilizing CAH . Treatment was started using hydrocortisone at dose of 10 mg/m2, at outpatient basis and being followed up regularly every month in pediatric endocrinology clinic.

EVIDENCE-BASED CRITICAL APPRAISAL

CASE

A 4 years-old boy was referred from BM Private Hospital to Endocrine Outpatient Department of Prof Ngoerah's Hospital , with chief complaint of growth of pubic hair since 5 month before consultation and penis enlargement with prepubertal testes and facial acne since age of 3 years. His voice also changed to be more like an adult male voice. Patient was born from healthy and non-consanguineous parents with 39-40 weeks of gestational age by C-section, due to breech position. Weight and height of birth was 2700 grams and 50 cm, respectively. He was born vigorously and was sent home 2 days after delivery. There was no history of repeated vomiting, dehydration or extreme muscle weakness. Family history of ambiguous genitalia was denied. There was no history of hormonal treatment and genetic abnormalities in the family. Physical examination revealed an alert boy, who looked very active, with normal physical examination.
Prader staging and virilization of genitalia eksterna was stage V with a normally formed penis with the urethral opening at the tip and prepubertal testes and genitalia externa was

virilitation with pubic hair. Tanner Stage of the patient was : Tanner Stage III, G1P3. Blood tests were done showed 17-OHP of 196.03 ng/ml (n: <= 0.90ng/ml), high level of testosterone at 270.1 ng/ml (n: <= 0.19ng/ml), level of B-HCG : <2.3mIU/ml, low level of LH : 0.1 mIU/ml (n: >0.6 mIU/ml), and low level of FSH: 0.1 mIU/ml (n: 0-5.0mIU/ml). Serum sodium and potassium were normal with value of 138 and 3.7 respectively, his bone age was equal to that of 14 years old male and upper abdomen ultrasound revealed a picture of hyperplasia of left adrenal gland.
Based on the clinical manifestations, laboratory findings, and radiology imaging, patient was then diagnosed with Peripheral Precocious puberty with classic simple virilizing CAH. Treatment was started using hydrocortisone at dose of 10 mg/m2, at outpatient basis and being followed up regularly every month in pediatric endocrinology clinic.

PROBLEMS

1. In children with Simple Virilizing CAH, what is the optimal regimen time for giving hydrocortisone which will prevent early puberty but not inhibit growth outright?

PROBLEM

PICO

P (*Patient/Problem*) : children with Simple Virilizing CAH
I (*Indicator*) : twice daily hydrocortisone regimen
C (*Comparation/Control*) : three times daily hydrocortisone regimen
O (*Outcome*) : optimizing adrenal control

CLINICAL QUESTION

In children with Simple Virilizing CAH, is twice daily hydrocortisone regimen compared to three times daily hydrocortisone regimen better in optimizing adrenal control?

JOURNAL SEARCHING STRATEGY

Keywords: glucocorticoids AND Congenital Adrenal Hiperplasia AND prepubertal growth and metabolic impacts

RESULT

Twice Daily Compared to Three Times Daily Hydrocortisone in Prepubertal Children with Congenital Adrenal Hyperplasia

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ABSTRACT

Introduction: Glucocorticoid therapy in children with congenital adrenal hyperplasia (CAH) must be finely balanced between optimizing adrenal control and minimizing side effects. Twice (BID) rather than three times daily (TID) hydrocortisone may provide similar adrenal control and reduce metabolic risk. We compared BID and TID regimens with respect to adrenal control, growth, and metabolic effects.
Methods: A retrospective chart review (n = 128 visits, 36 individual patients) of prepubertal children with classical CAH was conducted at a tertiary care center between March 2007 and February 2020. Adrenal control, growth, and metabolic data were extracted in those taking hydrocortisone BID versus TID. Univariate generalized estimating equations models were performed to analyze the effect of dose frequency on outcomes of interest.
Results: Overall, we found no difference in adrenal control (8% vs. 18% poor control) or testosterone levels (9.65 ng/dL vs. 7.62 ng/dL) between the BID versus TID groups. We

detected no difference in growth velocity (6.86 vs. 6.32 cm/year) or bone age advancement (11.3 vs. 5.91 months) between the groups. There was no difference in daily steroid dose (12.1 vs. 11.7 mg/m2/day), BMI Zscore (0.43 vs. 0.31), or systolic blood pressure percentile (65.5 vs. 61.7).
Conclusion: BID dosing provides similar adrenal control and does not appear to impact growth or bone age advancement. On the other hand, TID dosing does not appear to increase the metabolic side effect profile in this age-group. Dosing should be patient-centered with individualized consideration.

EVIDENCE-BASED CRITICAL APPRAISAL

(ASPECT OF CAUSATION)

Are the results of this study valid?	
1. Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?	Yes, there were clearly defined groups of patients, similar in all important ways other than exposure to the treatment.
2. Were treatments/exposures and clinical outcomes measured in the same ways in both groups?	Yes, treatments/exposures and clinical outcomes were measured in the same ways in both groups.
3. Was the follow-up of the study patients sufficiently long (for the outcome to occur in a large enough number of patients)?	Yes, study was conducted at a tertiary care center between March 2007 and February 2020.
4. Do the results of the study fulfill some of the therapeutic tests for causation? a. Is it clear that the exposure preceded the onset of the outcome? b. Is there a dose–response gradient? c. Is there any positive evidence from a "dechallenge–rechallenge" study? d. Is the association consistent from study to study?	a. Yes, It is clear that the exposure preceded the onset of the outcome. b. No, there is no dose-response gradient. c. No, there is no evidence from a "dechallenge–rechallenge" study. d. Yes, the association is consistent from study to study.
5. Does the association make biological sense?	Yes, the association makes biological sense.

This study is valid.

Are the valid results of this study important?

1.	What is the magnitude of the association between the exposure and outcome?	Outcome Good Poor BID 70 6 TID 41 9 CER : 0.18 EER : 0.92 ARR : 0.74 NNT : 1.35
2.	What is the precision of the estimate of the association between the exposure and the outcome?	CI 0.4565-0.6350

This study is important

Can we apply this valid, important evidence about causation aspect in caring for our patient?

1. Were the study patients similar to our own?	Yes, patients of study was similar with our patients
2. What are our patient's risks of benefit and harm from the agent?	Yes, the medication, facility, financial supports and human resources are available in our own setting.
3. What are our patient's preferences, concerns, and expectations from this treatment?	Yes. The patients and their families can accept the treatments according to their believes, and culture.

This study is applicable.

Conclusion: Valid, Important, and Applicable.

Level of evidence 2B with grade of recommendation B

Conclusion

We reported a case of peripheral precocious puberty with classic simple virilizing congenital adrenal hyperplasia in four years old boy with chief complaint of growth of pubic hair since 5 month before consultation, penis enlargement with prepubertal testes and facial acne since age of 3 years. There was no repeated vomiting, dehydration or extreme muscle weakness. Physical examination revealed an alert boy, who looked very active, with normal physical examinations, with sexual maturity rate is in tanner stage three.

Blood tests were done showed 17-OHP of 196.03 ng/ml (n: <= 0.90ng/ml),Serum sodium and potassium were normal with value of 138 and 3.7 respectively. With bone age was equal to that of 14 years old male. Upper abdominal ultrasound revealed a picture of hyperplasia of left adrenal gland.

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