



Peripheral Precocious Puberty Causes, Diagnosis and Management

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Design and settings: A retrospective hospital based study was conducted at King Khalid University Hospital (KKUH), Riyadh Saudi Arabia, during the period January 1990 and December 2016.

Materials and Methods: During the period under review, all patients with the diagnosis of peripheral precocious puberty were reviewed for age, sex, clinical characteristics, hormonal and radiological investigations.

Results: During the period under review; 19 patients were evaluated for PPP. Elevated levels of estradiol or testosterone levels with suppressed gonadotropin levels on GnRH stimulation test. Various etiological causes were noted, with congenital adrenal hyperplasia (8 patients) and hypothyroidism (5 patients) being the commonest. Adrenal tumors in 3 patients, ovarian pathology in two and McCune-Albright Syndrome was the diagnosis in one.

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Conclusion: Peripheral precocious puberty wasn't that rare in our series. Variety of causes with congenital adrenal hyperplasia and hypothyroidism were the commonest.

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I. INTRODUCTION

Precocious puberty (pp) is a common problem seen in pediatric endocrinology practice. It is a complex and can be classified into, central precocious puberty, gonadotropin dependent or true PP which results from early maturation of hypothalamo-pituitary- gonadal (HPG) axis, and peripheral (pseudo) precocious puberty which is also known as gonadotropin independent puberty, is the result of autonomous peripheral secretion of excess sex hormones independent of the HPG axis.(1-5)

The aim of this article was to discuss peripheral precocious puberty and its diagnosis and management.

II. MATERIALS AND METHODS

All patients diagnosed to have peripheral (pseudo) precocious puberty at the pediatric endocrine

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series of the King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia in the period January 1990 and December 2016, were retrospectively reviewed. Data included age, sex, clinical demographic data, hormonal and radiological investigations. The diagnosis was based on history, clinical examination, hormonal and radiological findings. Gonadotropin releasing hormone (GnRH) stimulation testing is considered as the gold standard for diagnosis (6-8). Radiological investigations (Pelvic Ultra Sonography), computed tomography (CT), and magnetic resonance imaging (MRI) were performed when indicated.

III. RESULTS

During the period under review a total of 19 patients were diagnosed to have peripheral (pseudo) precocious puberty.

Fifteen girls and 4 boys. Their mean age was 3.5 (range; 0.5-7 years). Laboratory investigations revealed elevated Oestradiol level, mean: 110 ng/ ml (normal; up to 35) and testosterone mean: 2.1 nanomol/ L (normal; 0.1-0.4) with suppressed gonadotropin levels on GnRH stimulation test. The etiological diagnosis showed variety of causes (Table).

Congenital adrenal hyperplasia and chronic hypothyroidism were the commonest found in eight and five patients respectively.

Tumors of the adrenal may cause virilization or feminization depending on whether androgens or estrogens are secreted, one estrogen secreting adenoma presented with feminization in a boy and two were due to adrenal carcinoma (figure).

Ovarian cyst and granulosa cell tumor were present in one patient each. The classic triad of polyostotic fibrous dysplasia, Café/ au/ lait macules of the skin and precocious puberty indicates McCune-Albright syndrome, found in one girl.

IV. DISCUSSION

Precocious puberty is defined as development of secondary sex characteristics before the age of eight years in girls and nine years in boys. Two types of precocious puberty are recognized; central (true) precocious puberty (CPP) and peripheral (pseudo) precocious puberty (PPP). CPP is caused by early activation of the hypothalamic-pituitary axes (HPA), with gonadotropin- releasing hormone (GnRh). Stimulated

gonadotropin secretion causing gonads maturation. In PPP, serum sex steroids are elevated independent of gonadotropin secretion, and because gonadotropin levels are low the gonads do not undergo maturation. Precocious puberty may be isosexual (involving secondary sex characteristics that are gender matched) or heterosexual (involving sex characteristics of the opposite gender). CPP is always isosexual, whereas PPP may be isosexual or heterosexual.

In Saudi Arabia where the prevalence of consanguinity increased (9,10), congenital adrenal hyperplasia commonly causes virilization without testicular enlargement in boys, and girls will not have breast enlargement, unless secondary central precocious occurred. Approximately 40% of our patients in this series were due to congenital adrenal hyperplasia (21- α -hydroxylase or 11- β hydroxylase deficiency which is a common occurrence in Saudi Arabia and easily diagnosed. The treatment includes glucocorticoids, usually hydrocortisone 12-15 mg/m²/day(11,12). Severe chronic hypothyroidism rarely results in precocious puberty, and unlike other causes, is associated with skeletal and growth delay. The pathophysiology is uncertain, but it may be due to the intrinsic FSH activity if very high TSH levels. The signs of puberty is usually reversible with thyroxine therapy (13,14). Tumors of adrenal glands, ovary, or testes may cause virilization or feminization depending on whether androgen or estrogen are secreted. These rare neoplasia require surgery or chemotherapy both. Also, Human Chorionic gonadotropin (hCG) secreting tumors can cause precocious puberty in boys by stimulating Leydig cells to secrete testosterone. Unlike boys, girls with HCG secreting tumors generally do not develop precocious puberty. Both LH and FSH stimulation are necessary for ovarian activation. Rapid virilization suggests the possibility of an endocrine secreting tumor. In adrenal tumors, both testosterone and Dehydroepiandrosterone are usually markedly elevated. A raised serum HCG suggests an hCG secreting tumor. α -fetoprotein and carcinoembryonic antigen (CEA) are potentially useful markers of non-germinomatous germ cell tumors. Ultrasonography helps in delineating the different causes (15-17) ovarian cysts occur in 2.5% of pre-pubertal girls. Imaging studies (ultrasound help in differentiating benign/ malignant lesions. Cysts having few internal echoes suggestive of hemorrhages with separation/calcification is most benign and requires observation with follow up ultrasound in 1 to 2 months. Surgery may be required for large ovarian cyst (>20 ml) because of the risk of adnexal torsion. Aromatase inhibitors are used in the management of persistent cyst. Recurrent or persistent ovarian cyst with a solid component in imaging suggest ovarian tumors. Juvenile granulosa cell tumor was the most common ovarian neoplasia to present with precocious puberty (17-22). The McCune-

Albright Syndrome causes precocious puberty, primarily in girls. The classic disorder comprises the triad of polyostotic fibrous dysplasia, café-au-lait pigmentation, and gonadotropin independent precocious puberty. The disorder results from an activating somatic mutation in Gs, the protein that transduces the signal of many 7-transmembrane domain receptors, including gonadotropin receptors. Testolactone and other anti-estrogen like Fudrozole and Tamoxifen are effective in treating girls with McCune-Albright syndrome. Unfortunately, escaping from the effects of treatment may occur after one to three years. After years of exposure to estrogen, many of these girls enter central precocious puberty and require treatment with LHRH analogue (23-26).

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Conflict of interest

The authors have no conflict of interest to declare.

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REFERENCES RÉFÉRENCES REFERENCIAS

1. Sultan C (ed): Pediatric and Adolescent Gynecology. Evidence-Based Clinical Practice. 2nd, revised and extended edition. Endocr Dev. Basel, Karger, 2012, vol 22, pp 84-100.
2. Pouw IS, Drop SL, Ladée-Levy JV, Slijper FM. Tijdschr Kindergeneesk 1986; 54(3): 77-83.
3. Eugster EA: peripheral precocious puberty causes and current management hormone research 2007; 71(supp1); 64-7.
4. Carel JC1, Léger J. Clinical practice. Precocious puberty. N Engl J Med. 2008 29; 358(22): 2366-77.
5. Muir A. Precocious puberty. Pediatr Rev. 2006; 27(10): 373-81.
6. Oerter KE1, Uriarte MM, Rose SR, Barnes KM, Cutler GB Jr. Gonadotropin secretory dynamics during puberty in normal girls and boys. J Clin Endocrinol Metab. 1990; 71(5): 1251-8.
7. Resende EA1, Lara BH, Reis JD, Ferreira BP, Pereira GA, Borges MF. Assessment of basal and gonadotropin-releasing hormone-stimulated gonadotropins by immunochemiluminometric and immunofluorometric assays in normal children. J Clin Endocrinol Metab. 2007; 92(4):1424-9. Epub 2007 Feb 6.
8. Pasternak Y1, Friger M, Loewenthal N, Haim A, Hershkovitz E. The utility of basal serum LH in prediction of central precocious puberty in girls. Eur J Endocrinol. 2012 Feb; 166(2): 295-9. doi: 10.1530/EJE-11-0720. Epub 2011 Nov 14.

9. Saedi-Wong S, Al-Frayh A, Wong H.Y.H. Socio-Economic. Journal of Asian and African Studies 1989; 24: 247-252.
10. AL-Jurayyan NAM, Osman H The increased prevalence of congenital adrenal hyperplasia in Saudi Arabia.
11. The role of consanguinity and multiple siblings involvement. European journal for research and medical science 2015; 3(11): 31-34.
12. Al-Jurayyan NA1, Al-Herbish AS, Abo Bakr AM, Al-Rabeeah AA, Al-Samarrai Al, Jawad AJ, Patel PJ, Abdullah MA.
13. Congenital adrenal hyperplasia in a referral hospital in Saudi Arabia: Epidemiology, pattern and clinical presentation. Ann Saudi Med. 1995 Sep; 15(5): 447-50.
14. Al-Jurayyan NA. Congenital adrenal hyperplasia due to 11 beta-hydroxylase deficiency in Saudi Arabia: clinical and biochemical characteristics. Acta Paediatr. 1995 Jun; 84(6): 651-4.
15. Radaideh AM1, Nusier M, El-Akawi Z, Jaradat D. Precocious puberty with congenital hypothyroidism. Neuro Endocrinol Lett. 2005 Jun; 26(3): 253-6.
16. Anasti JN1, Flack MR, Froehlich J, Nelson LM, Nisula BC A potential novel mechanism for precocious puberty in juvenile hypothyroidism. J Clin Endocrinol Metab. 1995 Jan; 80(1): 276-9.
17. Chowdhuri S1, Dharmalingam M, Kumar KM. Adrenal tumor presenting as precocious puberty. Indian J Pediatr. 2001 Apr; 68(4): 351-2.
18. AL-Jurayyan NA Estrogen-Secreting adrenocortical adenoma causing gynecomastia in a pre pubertal boy. Saudi Medical Journal 1995; (6,2), 75-78.
19. Jean CC, Juliane L Precocious puberty N Eng JM 2008 358: 2366-77.
20. De Sousa G1, Wunsch R, Andler W. Precocious pseudopuberty due to autonomous ovarian cysts: a report of ten cases and long-term follow-up. Hormones (Athens). 2008; 7(2): 170-4.
21. Gideon DS, Rainer W, Werner A. Precocious pseudo puberty due to autonomous ovarian cyst. A report of ten cases and long term follow up. Hormones 2008; 7: 170-4.
22. Sekkate S1, Kairouani M, Serji B, Tazi A, Mrabti H, Boutayeb S, Errihani H. Ovarian granulosa cell tumors: a retrospective study of 27 cases and a review of the literature. World J Surg Oncol. 2013 Jun 18; 11: 142. doi: 10.1186/1477-7819-11-142.
23. Haroon NN, Agarwal G, Pardey R, Dabadgha P, juvenile granulosa cell tumor presenting as isosexual precocious puberty a case report and review of literature. Indian J Endocrinology Metal 2012 17: 157-9.
24. Eugster EA. Peripheral precocious puberty: causes and current management. Horm Res. 2009 Jan; 71 Suppl 1: 64-7. doi: 10.1159/000178041. Epub 2009 21.
25. Mobini M, Vakili P, Vakili S McCune-Albright syndrome. A case report and literature review. Int J Pediatrics 2014 2(2): 153-6.
26. Weinstein LS1, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM.
27. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med. 1991; 12; 325(24): 1688-95.
28. Feuillan PP1, Jones J, Cutler GB Jr. Long-term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. J Clin Endocrinol Metab. 1993; 77(3): 647-51.
29. Mieszczyk J1, Eugster EA. Treatment of precocious puberty in McCune-Albright syndrome. Pediatr Endocrinol Rev. 2007; 4 Suppl 4: 419-22.

Table 1: Etiology of peripheral, gonadotropin- independent, (pseudo) precocious puberty in 19 patients

Diagnosis	Male	Female
•congenital adrenal hyperplasia		
-21-α hydroxylase deficiency	-	3
-11 B – hydroxylase deficiency	2	3
•Hypothyroidism	1	4
•adrenal tumors		
-oestrogen- secreting adreno-cortical adenoma	1	-
-adreno- carcinoma	-	2
•ovarian cyst	-	1
•Granulosa cell tumor	-	1
•Mc Cune-Albright syndrome	-	1
Total	4	15

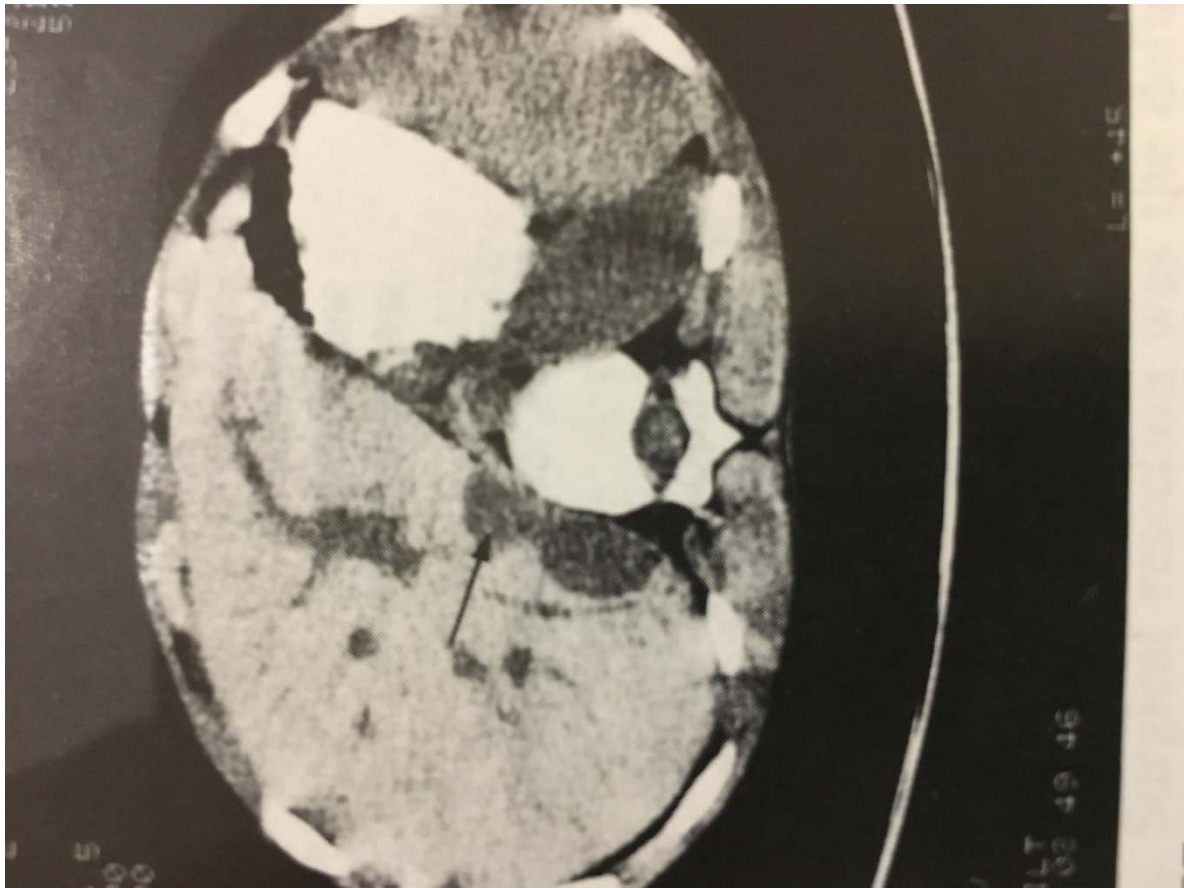


Figure 1: Computed tomography (CT) scan of abdomen reveals right adrenal mass which proved to be estrogen secreting abdomen.

