Precocious Pseudopuberty due to Ovarian Causes

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Background: It is important to differentiate central from peripheral causes of precocious puberty because of distinct management options. **Case Characteristics**: 4 girls with discordant pubertal development. **Observations**: All had low basal and GnRHa stimulated FSH & LH level with high estradiol level. Abdominal ultrasonogram helped in diagnosing precocious pseudopuberty- ovarian cyst in 3 children and juvenile granulosa cell tumour in one. **Outcome**: Case 1 and 4 underwent surgery in view of persistent cyst and tumor, respectively. Rest were managed conservatively. Regression of pubertal signs observed in all children during follow-up. **Conclusion**: Precocious pseudopuberty can be differentiated from central precocious puberty by GnRHa Stimulation test, bone age and abdominal ultrasound.

Keywords: *GnRHa stimulation test, Juvenile granulosa cell tumor, Ovarian cyst.*

Isosexual precocious puberty in girls is most commonly gonadotropin dependent (central) and often idiopathic. However, a discordant pubertal development (e.g., vaginal bleeding within 1 year of breast development) indicates peripheral causes of precocious puberty. The diagnosis of peripheral precocious puberty can be made based upon the Tanner staging, bone age, ultrasound imaging and most importantly, gonadotropin releasing hormone (GnRH) stimulation test.

CASE REPORTS

***Table* I** represent the details of the four children. All four children were born full term, appropriate for gestational age, never had a rapid growth spurt, and had no family history of sexual precocity. Bone age was not significantly advanced when compared with chronological age in all 4 patients. Elevated estradiol level with suppressed basal and GnRH analogue (GnRHa) stimulated gonadotropin levels were observed. Since GnRH is not easily available in our part of the country, we used GnRHa (Leuprolide acetate) 100 mg/m^2 subcutaneously. All children were followed up (average of 2 years).

Case 1 presented with breast development for 20 day and vaginal bleeding for 2 days and had ovarian cyst (3x2 cms) which enlarged over next 6 months follow-up (4.5x2 cms) and symptoms persisted. Hence right Oophorectomy was done which led to a histopathological diagnosis of benign ovarian cyst. Case 2 presented with breast development for 10 day and vaginal bleeding for 1 day. Had right ovarian cyst (3×3 cms) which regressed on follow-up. Case 3 presented with vaginal discharge and axillary hair growth for 4 months and had multiple cafe au lait spots and bilateral enlarged ovaries (>1mL) with left ovarian cyst (2×2 cms) suggestive of McCune-Albright Syndrome. Skeletal survey showed no evidence of fibrous dysplasia. Cyst regressed spontaneously during follow-up.

Case 4 presented with pubic hair for 2 month and vaginal bleeding for 2 days, and had a multiloculated cyst (8×3.7×7 cms) with thick internal echoes in right ovary suggestive of ovarian tumour. Tumour markers (AMH, inhibin AB, HCG, AFP, CA-125) were within normal limits. Right salphingoophorectomy revealed a Juvenile granulosa cell tumour in follicular pattern without vascular or capsular invasion. Peritoneal washings were negative for malignant cells (International Federation of Gynaecology and Obstetrics – FIGO stage 1). Child is currently doing well and pubertal signs have regressed on follow-up.

DISCUSSION

Precocious puberty (PP) has been defined as the onset of breast stage II development before the age of 8 years in girls [1]. It has to be differentiated from normal variant/ incomplete precocity (*e.g.* premature thelarche, premature pubarche, and premature menarche). It is usually classified as central precocious puberty (CPP), and peripheral/precocious pseudo puberty (PPP). If more than one sign of precocious puberty is present, or develops, or if the growth is accelerated, or bone age is significantly advanced (>2SD), it is unlikely to be a normal variant and warrants further investigations [2,3].

CPP is gonadotropin dependent (hence True PP). The sexual maturation is always complete and isosexual. CPP is more common than PPP and is most often idiopathic. Significantly advanced bone age (>2 SD), elevated (Pubertal level) estrogen, basal and GnRH stimulated gonadotropin levels (Predominat LH response) suggests CPP [4]. PPP is gonadatropin independent (hence

TABLE I CLINICAL AND LABORATORY FINDINGS

	Case 1	*Case 2*	*Case 3*	*Case 4*
Age	4 y	4 y 6 mo	2 y 6 mo	8 mo
Weight, kg (SD)	17 (0 to +1)	17 (0)	15.4 (+1 to +2)	9.1 (+1)
Height /length (SD)	102.8cms (0)	110cms (0 to +1)	94.2 cms (+1 to +2)	76 cms (+3)
SMR staging	Breast – Tanner 2	Breast – Tanner 2	Breast -Tanner 2	Breast – Tanner1
	Pubic hair – Tanner 1	Pubic hair – Tanner 1	Pubic hair – Tanner 1	Pubic hair – Tanner 3
Bone age	3 y 6 mo	5 y	2 y 6 mo	1 y
Estradiol (pg/mL)	40	25	23.92	98
Peak LH levels (mIU/mL)	0.1	0.1	0.3	0.1
Peak FSH levels(mIU/mL)	0.1	0.2	1.2	0.1
TSH (μIU/mL)	2.83	1.89	2.31	4.7
17 - OH P (ng/mL)	0.35	0.7	1.5	1.8

Pseudo/Peripheral PP). Maturation is most of the times incomplete/discordant with only one type of secondary sexual characteristic developing early. All subjects in our case study had discordant pubertal development. The causes of PPP are genetic (McCune-Albright syndrome, DAX1 mutations, etc.), adrenal (hyperplasia/tumours), ovarian (cyst/neoplasm), exogenous steroids and long standing untreated hypothyroidism. In most cases of PPP bone age may not be significantly (>2SD) advanced owing to shorter duration of symptoms [3]. Highly elevated oestrogen levels with low basal and GnRH stimulated gonadotropin levels suggests PPP.

Ovarian causes usually presents with isosexual precocity. Virilisation is seen in androgen producing ovarian neoplasms and adrenal causes. Adrenal causes are diagnosed by highly elevated DHEAS and 17 hydroxy progesterone levels [3]. Ultrasonogram will help further in delineating adrenal and ovarian causes. Long standing hypothyroidism is the only form of sexual precocity where growth retardation occurs [5].

Ovarian cysts occur in 2-5% of prepubertal girls. Imaging studies (Ultrasound) help in differentiating benign/malignant lesions. Cyst having few internal echoes suggestive of hemorrhage without septation/ calcification is mostly benign and requires observation with follow-up ultrasound in 4-8 weeks. Surgery may be required for large ovarian cysts (>20 mL) because of the risk of adnexal torsion [6,7]. Aromatase inhibitors are used in the management of persistent cyst [8]. Recurrent or persistent ovarian cyst with a solid component in imaging suggests ovarian tumour. Juvenile granulosa cell tumor was the most common ovarian neoplasms to present with precocious puberty. Elevated serum Inhibin and Anti-mullerian hormone were found to be a useful serum marker. Tumour staging (FIGO) is of greatest prognostic value. Surgery is the mainstay of treatment. Patient in case 4 had FIGO stage 1, carrying a favorable prognosis. Adjuvant chemotherapy is usually not indicated in this setting. Five-year-survival rate is more than 90% for FIGO stage 1 and 20-25% for advanced stages. Long term follow-up is necessary to detect recurrences early [9,10].

The current study documents a rare etiology of precocious puberty – Peripheral (Ovarian causes). Central precocious puberty can be differentiated from peripheral type by discordant/incomplete pubertal development, GnRH/GnRHa stimulation test and imaging studies. Benign ovarian cysts should be managed conservatively if the child is asymptomatic on follow up, thereby avoiding unnecessary oophorectomy. Suspect ovarian neoplasm in ovarian cyst with solid component or recurrence.

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REFERENCES

1. Bajpai A, Menon PS. Contemporary issues in precocious puberty. Indian J Endocrinol Metab 2011;15:S172-9.
2. Lee PA, Houk CP. Puberty and Its Disorder. *In:* Lifshitz F, editor. Paediatric Endocrinology. 5th *ed*. volume 2. USA. Informa Health Care; 2007.p. 273-303.
3. Fritz AM, Speroff L. Normal and Abnormal Growth and Pubertal Development. *In:* Sigafuse S, editor. Clinical Gynaecologic Endocrinology and Infertility. 8th ed. USA. Lippincott Williams & Wilkins; 2011.P. 391-434.
4. Berberoglu M. Precocious puberty and normal variant puberty: Definition, aetiology, diagnosis and current management. J Clin Res Pediatr Endocrinol. 2009;1: 164-74.
5. Baranowski E, Hogler W. An unusual presentation of acquired hypothyroidism: the Van Wyk-Grumbach

syndrome. Eur J Endocrinol. 2012;166:537-42.
6. Gideon DS, Rainer W, Werner A. Precocious pseudopuberty due to autonomous ovarian cysts: A report of ten cases and long-term follow-up. Hormones. 2008; 7:170-4.
7. Jean CC, Juliane L. Precocious Puberty. N Engl J Med. 2008;358:2366-77.
8. Nabhan ZM, West KW, Eugster EA. Oophorectomy in McCune-Albright syndrome: a case of mistaken identity. J Pediatr Surg. 2007;42:1578.
9. Schultz KAP, Schneider DT, Pashankar F, Ross J, Frazier L. Management of ovarian and testicular sex cord-stromal tumors in children and adolescents. J Pediatr Hematol Oncol. 2012;34:S55-S63.
10. Haroon NN, Agarwal G, Pandey R, Dabadghao P. Juvenile granulose cell tumour presenting as isosexual precocious puberty: A case report and review of literature. Indian J Endocrinol Metab. 2013;17:157-9.

Plasma Exchanges and Immunosuppression for Anti-complement Factor H Associated Hemolytic Uremic Syndrome

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Background: Atypical hemolytic uremic syndrome associated with autoantibodies to complement factor H is an important cause of acute kidney injury; most patients require dialysis and are at risk of progressive renal failure. **Case Characteristics:** 7 patients with gastrointestinal symptoms, acute kidney injury, thrombotic microangiopathy and elevated levels of anti-complement factor H antibodies. **Intervention**: Prompt initiation of plasma exchanges and immunosuppression. **Outcome**: Remission of hematological and kidney functions. **Message**: Prompt and specific management of antibody associated hemolytic uremic syndrome is associated with favorable outcome.

Keywords: *Corticosteroids, Hemolysis, Renal failure.*

Autoantibodies to complement factor H (CFH) are an important cause of atypical hemolytic uremic syndrome (HUS) in children, comprising 10-20% patients in cohorts from Europe and UK [1-3]. In a 6-year multicenter study on 246 patients with atypical HUS from India, we found high titers of anti-CFH antibodies in 56% cases [4]. Patients with anti-CFH associated HUS presented late, and had a relatively severe illness with prolonged oligoanuria, severe hypertension and prominent extra renal manifestations. The majority required renal replacement therapy and one-third had progressive kidney failure [3]. Although speculated that an infectious agent triggers formation of these antibodies in genetically susceptible hosts, no organism was identified.

During the months of January and February 2014, 7 patients were referred to us with HUS associated with anti-CFH antibodies. Given that this center normally takes care of 7-10 new patients with HUS annually, the increase in number of patients was unusual. We report their clinical features and outcomes.

CASE REPORTS

The clinical and laboratory features in 7 patients (3 girls), 5- to 11-yr-old, are shown in ***Table* I**. These patients presented with history of abdominal pain and vomiting followed by sudden onset of pallor and variable degree of jaundice and oliguria; none had hypertension. The diagnosis of HUS was based on presence of schistocytes in the peripheral smear, thrombocytopenia and elevated blood levels of creatinine. Six patients showed hypokalemia that persisted for 3-5 days. There was no history of diarrhea or any significant family history in all patients. Serology for leptospira, enteric fever, hepatitis A and E, and antinuclear antibody and antineutrophil cytoplasmic antibody were negative. Malarial parasite was not seen on smear examination. Anti-CFH antibody titers, estimated using ELISA [3], ranged between 880 and 16380 (normal <150) AU/ml. Low levels of complement C3 were present in six patients.

Following the diagnosis of HUS, plasma exchanges (filtration based, 1.5-volume) using fresh frozen plasma were initiated at a median of 9 days from onset of the illness. The plasma was dark brown during the first few exchanges, suggesting severe intravascular hemolysis. Each patient received daily plasma exchanges initially until hematological remission, followed by alternate day and finally twice weekly for total of 15-20 exchanges. The severity of renal failure was variable; peak creatinine