Original Article

Precocious puberty: An experience from a major teaching hospital in Central Saudi Arabia

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ABSTRACT

Precocious puberty is a developmental process that gives rise to secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. In general, precocious puberty can be classified as central or peripheral. This is a retrospective hospital-based study was conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, during the period January 1990 and December 2016. Data were abstracted from the medical records of patients diagnosed with precocious puberty, with special emphasis on age, sex, clinical characteristics, and relevant hormonal assay.

A total of 62 patients were diagnosed with Precocious Puberty (PP); 43 had Central Precocious Puberty (CPP) while 19 had peripheral precocious puberty (PPP). The majority of girls with CPP (68%) had idiopathic PP, while pathological causes were found in (50%) of boys. The commonest cause of PPP was congenital adrenal hyperplasia (42%) and chronic hypothyroidism (26%). In conclusion, this study showed that precocious Puberty is a common endocrine problem in our center. The etiology of CPP was idiopathic in the majority of girls while it was caused by CNS pathology in most of the boys in this cohort. Peripheral precocious puberty is not that rare and mainly caused by congenital adrenal hyperplasia or hypothyroidism.

Keywords: Precocious Puberty; Gonadotropin-Dependent; Gonadotropin-Independent; Saudi Arabia.

INTRODUCTION

Puberty is a period of physical, hormonal and psychological transition from childhood to adulthood, with accelerated linear growth and achievement

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of reproductive function [1]. It is a complex and a multifactorial process that includes genetic, metabolic, environmental, ethnic, geographic, and economic factors and results in the reactivation of hypothalamic-pituitary-gonadal (HPG) axis [2]. An effective pubertal onset requires pulsatile hypothalamic secretion of gonadotropin-releasing hormone (GnRH) [3-5]. GnRH Stimulates the secretion of gonadotropins (luteinizing hormone (LH), follicle stimulating hormone (FSH) by the anterior pituitary gland. Gonadotropin stimulates the gonads to secrete testosterone and estradiol [6-8]. And exerts a negative feedback effect on the hypothalamus. Also, testosterone and estradiol have a direct inhibitory effect on both the hypothalamus and the anterior pituitary gland [9]. This process is named gonadarche, which is often preceded by adrenarche [10]. Adrenarche isa process in which adrenocorticotropic hormone (ACTH), is independently responsible for the secretion of the androgens, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS). Adrenarche is clinically characterized by the development of axillary odor, and pubic and axillary hair [11-13]. The initial clinical manifestation of gonadarche is the development of the breasts in girls and the increase in testicular volume in boys. The classical definition of precocious puberty is the development of secondary sexual characteristics before the age of 8 years in girls and before 9 in boys [1]. Precocious puberty may be due to central or peripheral causes [1]. Central precocious puberty (CPP) is driven by the GnRH. It is diagnosed if the development of physical pubertal changes and the hormonal profile are consistent with normal puberty, but just occur earlier that it should be [2]. Peripheral precocious puberty means that GnRH does not drive the puberty. It is caused by either endogenous or exogenous secretion of sex hormones [1-8].

In this study, we aimed to highlight the various etiological causes of precocious puberty over more than 2 decades at a tertiary endocrine center in Saudi Arabia endocrine service at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia.

METHODS

In this retrospective study, we recruited all children with precocious puberty seen at the pediatric endocrine service, King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia over a 27 years’ period (January 1990 to December 2016). KKUH is the major teaching hospital of the King Saud University, which provides primary, secondary, and tertiary health care service for the local population as well as receiving a referral from other regions of the country. Data were abstracted from the medical records of the patients by two of the authors using a case report sheet. The data extracted included age, sex, clinical demographic date and relevant biochemical and radiological investigations. The diagnosis of precocious puberty and its types was according to the standard criteria [4,9-13].

STATISTICAL ANALYSIS

Statistical Package for Social Science (SPSS, Version 20) was used for the statistical analysis of the raw data. Mean and standard deviation were used for quantitative data while numbers and percentage were used for qualitative data. The level of significance was determined as P-value less than 0.05.

RESULTS

During the period under review, a total of 62 patients with precocious puberty were evaluated at the endocrine service in our center. Forty-six individuals were girls and 16 boys (Table 1). Central precocious puberty (CPP) resulting from activation of the hypothalamic-pituitary-gonadal axis was the diagnosis in 43 (69%) patients with a mean peak LH/FSH of 5.1 (post-GnRH stimulation). Thirty-one were girls (72.1%) and 12 (27.9%) boys. The majority (67.06%) of the girls were idiopathic while pathological in (50%) of boys (Table 2).

Peripheral (pseudo) precocious puberty (PPP) was the diagnosis in 19 (30.6%) with elevated sex-steroid hormone and suppressed gonadotropin, i.e gonadotropin-independent. Congenital adrenal hyperplasia and hypothyroidism were the commonest causes (42.1%, 26.3% respectively) (Table 3).

Other etiological causes included adenocarcinoma, adrenal adenoma, ovarian cyst, granulosa cell tumor and McCune-Albright syndrome.
Table 1- Demographic data of 62 patients with precocious puberty

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central precocious puberty</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>Age in years (mean)</td>
<td>3.8-6 (5.5)</td>
<td>2-7.5 (4.5)</td>
</tr>
<tr>
<td>Peripheral precocious puberty</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Age in years (mean)</td>
<td>2.5-8.7 (3.8)</td>
<td>0.5-6 (3.2)</td>
</tr>
</tbody>
</table>

Table 2- Etiology of central precocious puberty in 43 patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Arachnoid supra-sellar cyst</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>• Hypothalamic Hamartoma</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>• Craniopharyngioma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>• Dandy-walker cyst</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• Rathk’s cyst</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>• Head trauma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• Neurofibromatosis type 1 (NF-1)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>• Grade 4-intraventricular hemorrhage</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• Brain atrophy</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>• No neuroradiological studies</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 3- Etiology of peripheral precocious puberty in 19 patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 alpha hydroxylase deficiency</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>11 beta hydroxylase deficiency</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Adrenal adenoma (estrogen-secreting)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adreno-carcinoma</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Theca cell tumor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>McCune-Albright Syndrome</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>15</td>
</tr>
</tbody>
</table>
DISCUSSION

Precocious puberty (PP) is a common problem seen in pediatric endocrinology practice. Identification of a child with pathological pubertal development allows for an accurate diagnosis and application of current treatment strategies. Recent improvements in the diagnosis and management allow for a better outcome. It is crucial to decide whether the child has central (gonadotropin-dependent) or peripheral (gonadotropin-independent) form of precocious puberty. A systematic approach with a detailed history and clinical examination helps to arrive at an accurate diagnosis in most cases. A basal LH level is the best screening test to diagnose gonadotropin-dependent precocious puberty. LH level less than 0.1 IU/L indicates prepubertal stage. Stimulation tests using gonadotropin-releasing hormone (GnRH) or its analogs help to confirm the diagnosis of gonadotropin-dependent precocious puberty [14-18]. High-resolution magnetic resonance imaging (MRI) of the brain helps in detecting abnormalities in the hypothalamus and pituitary region. Central precocious puberty (true) (CPP) result from activation of the hypothalamic pituitary and referred to as LHRH-dependent precocious puberty was common in our study and account for 69%. The main etiology varies between different sexes. Idiopathic CPP occurs in 80% of girls in this study, while organic pathology was found in 45% of boys [19,20]. The underlying mechanism of the idiopathic CPP appears to be the same as that of normal puberty except for the earlier age of onset. Also, central nervous system (CNS) tumor can cause LHRH-dependent precocious puberty as in this series. Different CNS tumors including hypothalamic hamartoma were associated with precocious puberty in our patients as previously described by other authors [19-22]. Also, neurofibromatosis type 1 may lead to precocious puberty with or without an optic glioma [21,22]. Recently many genes including MKRN3 and KISSIR were implicated in the etiology of central precocious puberty CPP [23,24]. Unfortunately, none of our patients had molecular study of these genes. Peripheral precocious puberty (PPP), a gonadotropin-independent, is not that rare in our study and presented in 19 (30.6%) patients. Peripheral (pseudo) precocious puberty results from excessive secretion of gonadal or adrenal sex hormone. Congenital adrenal hyperplasia (CAH), is an autosomal recessive disorder that occurs commonly in our community which have high prevalence of consanguinity [25,26]. If the diagnosis of CAH is delayed this leads to an increase in the level of testosterone and a decrease in the level of gonadotropin and hence present with peripheral precocious puberty in girls. The classic form of congenital adrenal hyperplasia requires a glucocorticoid treatment [27-29]. Also, a tumor in the adrenal gland may cause virilization or feminization depending on whether testosterone or estrogen are secreted. This rare neoplasia may require surgery or chemotherapy or both [30-32]. Human chorionic gonadotropin (HCG) secreting tumor can also cause precocious puberty in boys by stimulating the Leydig cell to secrete testosterone. Another rare disorder, ovarian tumor or cyst causes feminization [33-36]. Also, McCune-Albright Syndrome (MAS) causes precocious puberty as in one of our patients. MAS consists of a triad of polyosteotic fibrous dysplasia, café-au-lait pigmentation, and gonadotropin-independent precocious puberty. MAS results from activating mutation in GNAS gene [36-38].

Severe hypothyroidism may rarely result in precocious puberty as in our series and unlike the other causes, is associated with skeletal and growth delay. The pathophysiology of precocious puberty in hypothyroidism is uncertain but it may be due to intrinsic follicle-stimulating-hormone (FSH) activity of very high TSH level [39,40]. The puberty is reversible with the thyroid hormone (thyroxine) administration.

In conclusion, precocious Puberty is a common endocrine problem in our center. The etiology of CPP was idiopathic in the majority of girls while it was caused by CNS pathology in most of the boys in this cohort. Peripheral precocious puberty is not that rare and mainly caused by congenital adrenal hyperplasia or hypothyroidism.
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REFERENCES