Primary Testicular Abnormalities
Causing Precocious Puberty Leydig Cell
Tumor, Leydig Cell Hyperplasia, and
Adrenal Rest Tumor

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ABSTRACT

The child with testicular enlargement in the absence of gonadotrophin stimulation presents a difficult diagnostic dilemma. Leydig cell tumors, Leydig cell hyperplasia, and tumors of adrenal rest tissue are the primary etiologic considerations. Because of considerable overlap in clinical presentation, careful biochemical and histologic evaluations are necessary to make the diagnosis. These should include serum levels of testosterone, dehydroepiandrosterone, androstenedione, 17-hydroxyprogesterone, and 11-desoxycortisol, as well as urinary levels of 17-ketosteroids. If diagnostic changes in the biochemical profile are not present, then testicular biopsy is indicated. Encapsulation, presence or absence of the crystalloids of Reinke, degree of seminiferous tubule maturation, and the site of any abnormal tissue are important observations in the examination of the tissue specimen. Once the diagnosis has been established, then appropriate and specific medical or surgical therapy can be instituted. With appropriate treatment, the long-term prognosis in each condition is good.

Introduction

The presence of penile and testicular enlargement in a boy under the age of 10 years presents the clinician with a challenging problem, both because of the complexity of the differential diagnosis and because of the presence of serious underlying pathology in approximately 60 percent of cases. Precocious puberty is usually divided into those showing gonadotropin release, often referred to as

* The views of the author are his own and do not purport to reflect the position of the Department of the Army or the Department of Defense.
matic changes. A list of the etiologic considerations in precocious puberty is presented in table I.

Three conditions must be considered in cases of virilization with testicular enlargement in the absence of gonadotropins. These include Leydig cell tumors of the testis, Leydig cell hyperplasia, and tumors of adrenal rest tissue in patients with congenital adrenal hyperplasia. Familial incomplete precocious puberty probably represents a variant of Leydig cell hyperplasia. Adrenal tumors do not cause testicular enlargement and will not be discussed in this paper. These entities present a very similar clinical picture but require very different treatment modalities. Thus, it is important to undertake a careful laboratory examination to assure an accurate diagnosis.

**Leydig Cell Tumors**

Leydig cell tumors represent 39 percent of non-germ cell tumors and 12 percent of all testicular neoplasms in childhood. They generally present in early to mid-childhood, with an average age at diagnosis of 4.7 years. Sexual precocity is usually accompanied by increased stature and muscle mass, as well as an advanced bone age.

The tumors are most frequently unilateral, but bilateral tumors have been reported. However, the asymmetry one might expect is often not found until well after virilization has been noted. Contralateral testicular enlargement with moderate Leydig cell and seminiferous tubule development has also been noted and ascribed to the effect of increased testosterone levels, and residual HCG secretion in the seminiferous tubules. Thus, the unilateral nature of the lesion often is not detectable at the time of presentation, owing to bilateral testicular enlargement.

Histologically, the tumors are highly variable. The crystalloids of Reinke are present in only about 30 percent of Leydig cell tumors in children. Most often the tumors are encapsulated, but cases have been reported without capsules and with seminiferous tubules interspersed in the apparent tumor mass. There are no increased mitotic figures nor other histologic evidence of malignancy. Thus, there exists a considerable overlap with cases of Leydig cell hyperplasia.

The biochemical profile is also somewhat variable. Testosterone is the major androgen secreted, and virtually all reported cases have had serum levels in the adult normal range. Androstenedione has been reported in a minority of cases and elevations in dehydroepiandrosterone (DHEA) have also been seen. Evidence of 11-hydroxylation may occur, although this is normally restricted to adrenal steroidogenesis. Urinary values are similarly variable and elevations of 17-ketosteroids have been reported. No increase in serum or urinary steroid production is seen after exogenous HCG stimulation.
In children, Leydig cell tumors are almost uniformly benign and therapy restricted to unilateral orchiectomy. Biopsy of the contralateral testes may be advisable in cases of bilateral enlargement, although bilateral tumors represent a minority of causes of contralateral involvement.

**Leydig Cell Hyperplasia**

Leydig cell hyperplasia is a recently defined condition which presents with precocious puberty. It may, however, represent the underlying condition in the kindreds reported with "idiopathic" or "familial" precocious puberty. In the kindreds evaluated for the presence of gonadotropins, none was found in a majority of cases. Serum levels of testosterone have been uniformly elevated to adult normal levels, although biologic assays were used in earlier reports. In two cases which were thoroughly studied, levels of adrenal androgens and metabolites were elevated for chronologic age but normal for the stage of pubertal development. Urinary 17-ketosteroids are often suppressed, at times even below normal prepubertal levels.

The histologic picture demonstrates variability from normal adult Leydig cell conformation to marked hyperplasia. Seminiferous tubule development may range from immature to the presence of mature spermatozoa. This latter fact has led to the previous assumption that follicle stimulating hormone (FSH) was present, despite documentation that no gonadotropins were present in these patients. Most probably, this represents the effects of increased testosterone levels, in the presence of low levels of locally secreted HCG, as previously noted in Leydig cell tumors.

Leydig cell hyperplasia is an essentially benign process. No Leydig cell tumors have been reported in the kindreds studied thus far. However, the advanced bone age present in these cases and ascribed to the action of prematurely elevated levels of testosterone frequently results in compromised adult stature. Currently, no proven therapy is available to halt the progression of bone age. However, recent data suggest that cyprotorene acetate may be therapeutically useful in this condition.

**Tumors of Adrenal Rest Tissue**

It is estimated that up to 50 percent of newborn males have islands of adrenal tissue in the testes. This so-called adrenal rest tissue usually atrophies during early infancy. In children with congenital adrenal hyperplasia, however, continued adrenocorticotropic hormone (ACTH) stimulation may result in hyperplasia of this tissue with subsequent increase in testicular size. Most commonly, these are patients with non-salt losing 21-hydroxylase deficiency, although 11-hydroxylase deficiency has also been reported.

The biochemical picture in these children is quite different than in the two previous conditions. Testosterone is not usually elevated significantly above normal prepubertal values. Dehydroepiandrosterone (DHEA) and androstenedione may be mildly to moderately elevated. Marked elevation of serum values of 17-hydroxyprogesterone (17-OHP) is present in 21-hydroxylase deficient children, as is 11-deoxycortisol in the children with 11-hydroxylase deficiency. In cases with elevations which may not appear diagnostic, the administration of a synthetic adrenocorticotropic hormone will result in more pronounced elevation of these metabolites in children with hydroxylase deficiencies. Urinary 17-ketosteroids are elevated in both conditions.

Treatment consists of the administration of corticosteroids, but it may require very high doses to cause regression of the
cellular hyperplasia. However, if regression does not occur despite evidence of biochemical correction, the testicular biopsy is indicated, as Leydig cell tumors have been reported in children with congenital adrenal hyperplasia (CAH). Appropriate treatment usually halts bone age advancement and, thus, can preserve normal adult stature.

Patient Evaluation

The initial evaluation of a patient with precocious puberty begins with a careful history and physical examination. Key points in the history include duration, family history, and history of erections or ejaculation. Duration is of great importance, as in long-standing cases the bone age may be advanced to a degree where spontaneous activation of the hypothalamic-pituitary axis may have occurred, causing release of LH and FSH, even though the underlying cause may be one of the incomplete precocious puberties. Family history may be positive in either Leydig cell hyperplasia or adrenal hyperplasia. No familial incidences of Leydig cell tumor has been reported. Erections suggest testosterone effect, and ejaculation indicates maturation of seminiferous tubules.

Physical examination should concentrate on testicular examination. Careful palpation should be performed to look for any asymmetry. Unilateral enlargement or discrepancy in the degree of enlargement suggest tumor, either Leydig cell or adrenal rest tissue. Multiple nodularities are usually indicative of adrenal rest tumors. The lack of asymmetry does not indicate hyperplasia as an etiology, since the tumors may yet be too small for palpation. Transillumination of the testes may help identify tumors that as yet are not clearly palpable.

Laboratory evaluation uniformly begins with examination of LH, FSH, and HCG levels. Once complete precocious puberty has been eliminated from consideration, examination of serum steroid profiles can provide the most useful data to establish the diagnosis. A brief summary of these profiles is presented in table II. Serum levels of DHEA, androstenedione, and urinary levels of 17-ketosteroids are quite variable and often may confuse rather than clarify the picture. In cases where the random levels of testosterone, 17-hydroxyprogesterone and 11-desoxycortisol do not clearly ascertain the diagnosis, ACTH stimulation or high dose dexamethasone suppression (1.25 mg per m² per d for five days) may give diagnostic changes to the profiles. Adrenocorticotropic hormone stimulation will accentuate the elevation of 17-hydroxyprogesterone or 11-desoxycortisol in adrenal etiologies while leaving the testosterone unchanged.

<table>
<thead>
<tr>
<th>TABLE II</th>
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<td>Biochemical Profiles</td>
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<tr>
<th></th>
<th>Leydig Cell Tumor</th>
<th>Leydig Cell Hyperplasia</th>
<th>21-Hydroxylase Deficient</th>
<th>11-Hydroxylase Deficient</th>
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<tbody>
<tr>
<td>Testosterone</td>
<td>++</td>
<td>++</td>
<td>NL to SI</td>
<td>NL to SI</td>
</tr>
<tr>
<td>Dehydroepiandosterone</td>
<td>NL to +</td>
<td>NL to +</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>+</td>
<td>+</td>
<td>NL to +</td>
<td>NL to +</td>
</tr>
<tr>
<td>Urinary 17-ketosteroids</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone</td>
<td>NL to SI</td>
<td>NL to SI</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>11-Desoxycortisol</td>
<td>NL to SI</td>
<td>NL to SI</td>
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Dexamethasone suppression will decrease these levels in adrenal rests, while leaving testosterone unchanged in Leydig cell abnormalities.\textsuperscript{13} Biopsy and histologic examination may be useful in differentiating Leydig cell tumor from hyperplasia and in patients with CAH in whom the palpable abnormalities do not regress under appropriate steroid therapy.\textsuperscript{3,5,15} A brief summary of histologic differences is presented in table III. The cellular structures of adrenal rest tissues and Leydig cells are similar, so that these comparatively gross measures provide needed information.\textsuperscript{15} This is not surprising given the similar embryologic etiology of each type of cell.\textsuperscript{3,5,13-15} The benign nature of Leydig cell tumors in childhood argues for biopsy of all such lesions prior to orchiectomy.\textsuperscript{3-4,5-6,7-10,13} Reports of difficulty in suppression of adrenal rests further support this approach.\textsuperscript{15}

Summary

Precocious puberty involves a long and complex differential diagnosis. In males, over 60 percent have serious underlying pathology. In the absence of gonadotrophins, the primary considerations are Leydig cell tumor, Leydig cell hyperplasia, and adrenal rest tumor. These present clinically in very similar manners and laboratory evaluation is necessary for accurate diagnosis.

A biochemical profile should include serum levels of testosterone, DHEA, androstenedione, 17-hydroxyprogesterone, and 11-desoxycortisol, as well as urinary 17-ketosteroids. Leydig cell abnormalities will show marked increase in testosterone, while adrenal rest tumors will show elevated levels of urinary 17-ketosteroids and serum DHEA. Androstenedione levels can help differentiate Leydig cell tumor from hyperplasia. The level of metabolic block in adrenal rest tumor can be ascertained from the relative levels of 17-hydroxyprogesterone and 11-desoxycortisol. Dexamethasone suppression or ACTH stimulation can be used to accentuate changes in the biochemical profile in uncertain cases.

Histologic examination of a testicular biopsy is indicated in cases which remain unclear, particularly prior to any contemplated orchiectomy. Encapsulation, seminiferous maturation, presence of Reinke’s crystalloids, and site of the abnormality vary in each condition but may provide the additional information necessary for accurate diagnosis.

Therapy is medical in patients with adrenal rest tumors (steroid suppression) or Leydig cell hyperplasia (observation or cyproterone acetate). Surgical intervention, usually restricted to simply orchiectomy, is indicated only in cases of Leydig cell tumor. With appropriate therapy, the long-term prognosis in all three conditions is good.

**TABLE III**

<table>
<thead>
<tr>
<th>Encapsulation</th>
<th>Leydig Cell Tumor</th>
<th>Leydig Cell Hyperplasia</th>
<th>Adrenal Rest Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually present</td>
<td>Not present</td>
<td>Present occasionally</td>
<td>Absent</td>
</tr>
<tr>
<td>Crystalloids of Reinke</td>
<td>Present in 30%</td>
<td>Usually absent</td>
<td>Mature</td>
</tr>
<tr>
<td>Seminiferous tubules</td>
<td>Maturation</td>
<td>Maturity</td>
<td>Immature</td>
</tr>
<tr>
<td>Site</td>
<td>Localized intratesticular</td>
<td>Diffuse intratesticular</td>
<td>May be peritesticular</td>
</tr>
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**References**


