A Female Case of the HCG-Producing Ectopic Pinealoma Associated with Precocious puberty

Reiko Demura, Hiroshi Demura, Kazuo Shizume, *Osami Kubo, and *Koichi Kitamura

Department of Internal Medicine, Tokyo Women's Medical College, Tokyo 162 and *Department of Neurosurgery, Neurosurgical Institute, Tokyo Women's Medical College, Tokyo 162

Synopsis

A female case of precocious puberty associated with HCG-producing ectopic pinealoma was reported. The patient, a 5-year-old girl, was referred to the hospital because of headache and choked discs. Physical examination revealed normal physical growth with breast enlargement. Endocrinological study revealed a high plasma HCG concentration of 1192 ng/ml with a normal FSH level. None of HCG, LH and FSH did respond to the LH-RH test. A partial resection of the tumor and an external X-ray irradiation relieved the symptoms and breast enlargement subsided with a remarkable decrease in the plasma HCG level. Histological examination revealed two-cell-pattern pinealoma and electron microscopic findings showed abundant secretory granules in the dark cells. HCG content in the tumor was as high as 400 ng/mg of acetone dried tumor tissue, but no FSH was detectable. Hitherto, all of the reported cases of precocious puberty associated with pineal tumors have been exclusively boys. A normal level of plasma FSH concentration with a somewhat elevated prolactin level might be a contributory factor for the development of precocial sexual development in the present case.

The nature of the precocious puberty associated with pineal tumors has been controversial. Recent studies demonstrated the ectopic human chorionic gonadotropin (HCG) production in some of the two-cell-pattern pinealoma and gave a direct explanation for the association of these two disorders. However, this still does not offer any explanation for the exclusive occurrence of the precocious puberty associated with pineal tumors in boys.

We experienced a female case of ectopic pinealoma associated with precocious puberty manifested as premature theralche, in which ectopic HCG production was clearly demonstrated. Endocrinological aspects of this particular case will be discussed.

Materials and Methods

Case Report

K. U., a 5-year-old girl, was admitted to the hospital because of headache. She had a generalized convulsion 8 months before admission, since then she started to complain of headache, which gradually became severe. She was found to have choked discs by a pediatrician and was referred to our neurological department. Physical examination revealed a somewhat drowsy girl with the normal physical growth for her age. Bone age was 5 years. Breast enlargement (Tanner grade 2) was noted on both sides as shown in Fig. 1. The mammary gland was palpable and slightly tender but no nipple discharge was noted. No axillary and pubic hair were noted. She has not experienced menarche and no clitoral enlargement was noted.

Laboratory data revealed normal urinalysis, CBC and serum electrolytes. A roentgenogram of the skull showed diastasis of the sutures and erosion of the sella turcica. Right brachial angiogram revealed
unrolling of the anterior cerebral artery, stretching of the anterior choroidal, kenticulostriate and thalano-
perforating arteries. A dimer ventriculogram revealed
a defect of the anterior third ventricle but no ab-
normalities in the recessuses pinealis and suprapinealis.

The patient underwent a ventriculo-peritoneal shunt
construction on the fifth day in hospital and a partial
resection of the tumor was performed thereafter.
An external X-ray irradiation with a total focal dose
of 4350 rads was given. Breasts subsequently re-
gressed rapidly by the time of the completion of
the radiation therapy.

Histologically, a light microscopic examination
showed a typical two-cell-pattern pinealoma (Fig. 2).
The electron microscopic findings showed both of
the clear and dark cells with abundant secretory
granules of about 500 nm in diameter in the dark
cells (Fig. 3).

Methods

Plasma luteinizing hormone (LH) and follicle sti-
mulating hormone (FSH) were measured by radio-
immunoassay (RIA) by the use of RIA kits of
Daichi RI laboratory with a reference standard of
2nd IRP-HMG (mIU/ml). Plasma HCG was measured
by RIA by the use of RIA kit for HCG made by CIS
and distributed by Midorijuji Co., and expressed as
ng/ml (1 mg is equivalent to 6600 IU of the 2nd
IS. HCG). LH and HCG crossreacted unspecifically
each other, and LH kit measured HCG about \( \frac{1}{2} \) of
LH, and HCG kit measured LH about \( \frac{1}{3} \) of HCG.
Plasma prolactin was measured by RIA by the use
of Friesen \#2 kit, which was a kind gift by NIH.
Plasma estradiol and testosterone were measured by
RIA by the use of antisera raised in our laboratory.
Tumor content of HCG and FSH were determined by RIA after the extraction of the acetone-dried tumor tissue with a modification of Hartree's method (Hartree, 1966).

LH-RH and TRH test was performed by i.v. administration of 100 µg of LH-RH mixed with 10 µg/kg of TRH at fasting and blood samples were drawn before, and 30, 60, 90 and 120 min, after the injection.

**Results**

Basal plasma levels of various hormones before and after treatment were shown in Table 1. HCG and LH were found to be elevated before treatment but both of them

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Normal Range</th>
<th>Before treatment</th>
<th>1 month after treatment</th>
<th>4 months after treatment</th>
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</thead>
<tbody>
<tr>
<td>HCG</td>
<td>n.d.</td>
<td>1192 ng/ml</td>
<td>14.0</td>
<td>—</td>
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<tr>
<td>LH</td>
<td>2.8-5.4 mIU/ml</td>
<td>306.2</td>
<td>7.6</td>
<td>7.6</td>
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<tr>
<td>FSH</td>
<td>2.4-6.6 mIU/ml</td>
<td>8.9</td>
<td>1.0</td>
<td>6.7</td>
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<tr>
<td>Prolactin</td>
<td>2-20 ng/ml</td>
<td>31.8</td>
<td>22.0</td>
<td>19.0</td>
</tr>
<tr>
<td>TSH</td>
<td>1-6 µU/ml</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>GH</td>
<td>1-6 ng/ml</td>
<td>3.2</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Estradiol</td>
<td>&lt;20 pg/ml</td>
<td>n.d.</td>
<td>n.d.</td>
<td>—</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;6 ng/dl</td>
<td>40</td>
<td>8.0</td>
<td>—</td>
</tr>
</tbody>
</table>

Fig. 4. Responses of plasma HCG, LH, FSH, prolactin and TSH to the LH-RH and TRH test before and after treatment. Solid lines indicate those before treatment, and dotted lines indicate those after treatment.
decreased rapidly shortly after treatment. Basal levels of FSH were in normal height for her age both before and 4 months after treatment, but was low 1 month after treatment. Estradiol was not detectable both before and after treatment. Testosterone was slightly high for her age before treatment, but returned to normal after treatment. Figure 4 showed the responses of plasma HCG, LH, FSH, prolactin and TSH to the LH-RH and TRH test. None of HCG, LH and FSH did show the response to LH-RH both before and after treatment. Prolactin showed a somewhat blunted response with a slightly elevated basal level before treatment, but showed a normal response with a decreased basal level after treatment. Tumor content of HCG was 400 ng/mg of acetone-dried tumor tissue, but FSH was not detectable.

**Discussion**

It was clearly demonstrated that the present case was a gonadotropin-producing ectopic pinealoma, from a clinical course, endocrinological studies and a histological examination. Furthermore, in spite of a crossreactivity of LH and HCG, it could be concluded that an elevated gonadotropin was HCG, from the fact that the values measured as HCG were exceedingly higher than those as LH in all of the samples measured.

The diagnostic criteria of the ectopic hormone producing tumor were satisfied in the following points; firstly, a demonstration of the elevated plasma HCG and a presence of premature theralche, a clinical symptom attributable to the increased HCG production, secondly, a demonstration of high HCG content in the tumor tissue, thirdly, a disappearance of breast enlargement with a markedly decreased plasma HCG level after treatment and finally, a demonstration of the secretory granules in the tumor tissue by an electron microscope.

It is quite fascinating to consider a mechanism of the development of precocious puberty in association with intracranial HCG-producing tumors, in view of its exclusive occurrence in boys. Mori *et al.* speculated that the coexistence of FSH with LH should be necessary for precocial sexual development in girls, but not in boys (Mori *et al.*, 1974). Decreased or undetectable levels of plasma FSH have been reported in most of the subjects with HCG-producing tumors (Reiter *et al.*, 1971, 1973). FSH suppression in the presence of an increased amount of HCG was explained either by negative feedback suppression by gonadal steroids (Reiter, 1972), or by direct short feedback suppression (Hirono *et al.*, 1972). Furthermore, the suppressibility of FSH seemed to depend on the amount of HCG. It was demonstrated that FSH levels varied inversely with a total gonadotropin secretion in men with gonadotropin-secreting testicular tumors (Reiter *et al.*, 1971).

Taking these in consideration, the present case was quite characteristic because of a FSH level compatible with that in normal subjects for her age. Ectopic production of FSH associated with HCG from the tumor was ruled out by a measurement of FSH in the tumor. Interference of the FSH assay by an increased amount of HCG was also negligible as the specificity of the FSH radioimmunoassay method had been fairly established.

The possibility was that the suppression of FSH was not operative in the present case, firstly because of the very rapid onset and short duration of the disease, or secondly because of HCG with less biological activity. It has been demonstrated that a subunit devoid of biological activity was a main product in some of the ectopic HCG-producing tumor (Vaitukaitis, 1973). The third possibility was a lack of humoral substances which might be necessary to effect FSH suppression in addition to estrogen as suggested
by Reiter (Reiter et al., 1973). Unfortunately, none of the above possibilities were proven in the present case at this point. The temporary suppressed FSH level 1 month after treatment may be explained by a suppressible effect of a fairly large amount of corticosteroids given for a postoperative period on the gonadotropin secretion.

Plasma estrogens were not detectable in the present case. This may reflect the limit of the assay sensitivity, therefore a slight and temporal increase in estrogen secretion could not be denied. A slightly elevated testosterone level suggested an increased ovarian secretion of the precursor steroids. Wilkins et al. stated that the breast tissue having a lower threshold of response to estrogens than the other female sex organs and premature theralche occurred easily with low levels of estrogens (Wilkins et al., 1965).

It is still puzzling whether the precocious puberty developed in this girl if a plasma level of FSH was suppressed as in the ordinar cases of HCG-producing tumors. Although, Albert demonstrated a considerable FSH action of HCG (Albert, 1969), the necessity of the coexistence of FSH with HCG remains to be elucidated for precocious sexual development in girls.

Elevated prolactin might favor the development of breast enlargement in the present case. This may indicate a hypothalamic invasion of the tumors and suggest a possible contributory role of the hypothalamus to the development of precocious puberty.

At all events, this was the first case of precocious puberty manifested as premature theralche in a girl associated with ectopic pinealoma.

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