Familial hypothalamic hypogonadotropic hypogonadism

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Summary: Clinical findings and endocrine studies are reported concerning six subjects (from two pedigrees) suffering from isolated hypogonadotropic hypogonadism. Their complete lack of any gonadotropin response to clomiphene stimulation, together with positive responses of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to LH-releasing hormone stimulation (LH-RH) provide evidence for a hypothalamic basis for this disorder. Additional data are presented indicating that variables such as circulating estrogen levels may influence the gonadotropin response to LH-RH.

Résumé: Hypogonadisme hypogonadotrope hypothalamic familial

L'étude de six membres de deux familles présentant un tableau d'hypogonadisme hypogonadotrope sélectif a permis d'impliquer l'hypothalamus dans la genèse du syndrome.

Les taux abaissés de FSH et de LH, en présence de fonctions thyroïdiennes, corticotrope et somatotrope normales, ont permis de poser un diagnostic d'hypogonadisme hypogonadotrope hypothalamique sélectif.

Une stimulation par du clomiphène (200 mg/jr x 7 jr) n'a pas amené d'augmentation des gonadotrophines. Par ailleurs, une réponse appréciable de FSH et de LH à des stimulations par 50 et 500 µg de LH-RH a permis de préciser l'intégrité de l'hypothalamus et de situer la pathogénèse du syndrome au niveau de l'hypothalamus.

Il semble de plus qu'un prétraitement avec des œstrogènes peut diminuer la réponse des gonadotrophines à la stimulation par LH-RH.

Familial hypogonadotropic hypogonadism may occur alone1,4 or in association with several genetic syndromes, such as Kallmann’s syndrome (with anosmia) and the Laurence-Moon-Biedl syndrome, or with congenital ataxia or ichthyosis.1,4 The demonstration that patients with Kallmann’s syndrome show significant FSH and LH responses to stimulation with LH-releasing hormone (LH-RH) is evidence for an underlying inherited hypothalamic or higher neural defect in this syndrome.10 This report describes the endocrine features in six members of two pedigrees affected with isolated hypogonadotropic hypogonadism in whom there also appears to be an underlying hypothalamic defect.

Case reports

The pedigrees for these two French-Canadian families are shown in Fig. 1. The families were not related and there was no known consanguinity. Endocrine and olfactory testing were not carried out in unaffected relatives.

Family A

The proband, G, had received two years of androgen therapy five years previously because of sexual infantilism. When seen at age 23 he was 178 cm tall and had a eunuchoid body habitus, a penis of normal size, scanty sexual hair, a small prostate, and testes which measured only 1.5 cm in their longest diameter. There was no gynecomastia. His bone maturation was adult. An earlier testicular biopsy had been interpreted as showing "infantile" testicular development. His sister, J, presented with primary amenorrhea at age 19. Her height was 168 cm; she had no breast development and only scant pubic hair. Laparoscopy disclosed a uterus of prepubertal size and small smooth ovaries. A brother, Y, when examined at age 17, was also sexually infantile with small testes, was 159 cm tall and had a bone age of 13 years. A testicular biopsy revealed small immature seminiferous tubules without active spermatogenesis and no recognizable Leydig cells. The older sister, M, remained eunuchoid.

Family B

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FIG. 1—Pedigrees of two families with isolated hypogonadotropic hypogonadism.

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sexually infantile until age 29, at which time pubic hair growth and breast development began spontaneously. When examined at age 33 she had Tanner\textsuperscript{11} stage B\textsubscript{3} breast development and adult pubic and axillary hair. Laparoscopy disclosed a small uterus and small smooth ovaries.

The findings on neurological examination, including olfactory testing, were within normal limits in all subjects except M, who had scoliosis and atrophy of the lower limb muscles as a result of paralytic poliomyelitis at age 10. Routine hematological and serum biochemical parameters, skull x-rays, electroencephalograms and lymphocyte karyotypes were normal in all subjects. All seven living siblings had undergone a normal puberty and were sexually developed and fertile.

**Family B**

The proband, D, presented at age 18 with primary amenorrhea, absent breast development and scant pubic and axillary hair. Her bone age was 14 years and her height 151.5 cm. Laparoscopy revealed an infantile uterus and small smooth ovaries. Her younger sister, B, also first seen at age 18, was 158 cm tall and sexually infantile. Her bone age was 12 years. In both girls neurological examination, including olfactory testing, showed no abnormality. Blood chemistry and skull x-rays were normal and lymphocyte karyotypes were 46.XX. An older sister had undergone normal puberty at age 13 and the youngest sister (age 3 years) is still prepubertal.

In all six subjects of both families serum thyroxine and diurnal cortisol concentrations were within normal limits. All showed a normal prepubertal serum growth hormone response to insulin hypoglycemia (peak GH greater than 5 ng/ml), and all had a normal urinary hydroxycorticoid response to oral metyrapone stimulation. The four members of family A all failed to show a rise in serum cortisol concentration during insulin hypoglycemia; this response was normal in the two subjects of family B.

**Materials and methods**

Serum concentrations of FSH\textsuperscript{12} and LH\textsuperscript{13} were measured by radioimmunoassay, using the pituitary standard LER-907 (supplied by the National Pituitary Agency of the National Institutes of Arthritis and Metabolic Diseases). Serum testosterone was measured by a competitive protein-binding method,\textsuperscript{14} and estradiol by radioimmunoassay.\textsuperscript{15} Cis-clomiphene (a gift of Dr. D. Holtkamp, Merrel-National Laboratories) was given to each subject except B in a dose of 50 mg four times a day for seven days, with blood samples being obtained on days 0, 3 and 7. Synthetic LH-RH (Ipyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH\textsubscript{2}) was a gift of Dr. G. Rochefort, Ayerst Pharmaceutical Company. Blood samples were obtained by means of an indwelling catheter immediately before the rapid intravenous administration of LH-RH (time 0), and 15, 30, 45, 60, 75 and 90 minutes later. Each subject in Family A received initially 50 \textmu g of LH-RH. Two days later subjects J and M, and also the family B subjects (D and B) were tested with 500 \textmu g LH-RH. Both test doses were then repeated in J and M following seven days of treatment with conjugated estrogens (Premarin\textsuperscript{®} 1.25 mg/day). All results were analysed by a factorial analysis of variance.

**Results**

The ranges of pre-stimulation serum concentrations of gonadotropins and gonadal steroids are shown in Table I. While these clinically hypogonadal subjects showed below-normal FSH and LH levels in most specimens, it should be noted that in each subject at least one value of FSH and/or LH was found within the normal adult range. Serum testosterone levels were in the range seen in adult females or castrate males. Serum estradiol concentrations were undetectable except for one value (0.9 ng/dl) in M, who had some spontaneous breast development.

The absence of either an FSH or an LH response to clomiphene stimulation in the five subjects tested is shown in Fig. 2, contrasted with the brisk FSH and LH response seen in healthy adult males. None of the hypogonadal subjects showed a testosterone or estradiol response to clomiphene, in contrast with the normal subjects, who showed a significant rise in both (data not shown).

The results of LH-RH stimulation, using an intravenous dose of 50 \textmu g, are shown in Fig. 3. All four subjects tested

### Table I—Serum gonadotropin and gonadal steroid concentrations* in hypogonadotropic subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>FSH (\textmu g/dl)</th>
<th>LH (\textmu g/dl)</th>
<th>Testosterone (ng/dl)</th>
<th>Estradiol (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>M</td>
<td>23</td>
<td>7.3-7.5</td>
<td>1.1-3.6</td>
<td>40-60</td>
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<tr>
<td>J</td>
<td>F</td>
<td>19</td>
<td>&lt;2.0-6.8</td>
<td>1.6-2.6</td>
<td>35-46</td>
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<tr>
<td>Y</td>
<td>M</td>
<td>17</td>
<td>5.0-8.4</td>
<td>1.9-3.4</td>
<td>30-41</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>M</td>
<td>F</td>
<td>33</td>
<td>4.8-8.9</td>
<td>1.8-2.1</td>
<td>13-16</td>
<td>&lt;0.5-0.9</td>
</tr>
<tr>
<td>D</td>
<td>F</td>
<td>18</td>
<td>6.0-10.5</td>
<td>1.6-2.5</td>
<td>-</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>B</td>
<td>F</td>
<td>18</td>
<td>5.3-13.3</td>
<td>1.1-3.1</td>
<td>12</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Normal adult M 20-40 8.0-30.0 3.5-7.5 260-1100 0.3-3.8

Normal adult F 20-34 10.0-55.0 2.4-45.0 10-75 0.8-25.0

*Range of two to six determinations.

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12.
showed a significant rise in serum LH levels, with peak levels attaining low-normal adult LH concentrations. Only three subjects showed an FSH response to this dose, and again these reached the low-normal adult range. There was no sex difference apparent in the responses to this dose.

With the larger 500-µg dose of LH-RH, all four subjects showed both FSH and LH responses; in J and M the FSH response to the 500-µg dose was significantly greater than to the 50-µg dose (F=80.7; P<0.001); the LH responses were similar at the two dose levels. In Fig. 4 these results are compared with the response seen in a group of healthy males. Control LH levels and the magnitude of the LH response to LH-RH were significantly below normal in the hypogonadotropic subjects (F=72.0; P<0.001). No significant difference in the mean FSH response to LH-RH was apparent.

The effect of one week of pretreatment with conjugated estrogens upon the gonadotropin response to 50 and 500 µg LH-RH in subjects J and M is shown in Table II. Premarin pretreatment caused a significant reduction in both the FSH (F=86.4; P<0.001) and the LH responses (F=16.6; P<0.01).

**Discussion**

The diagnosis of hypogonadotropic hypogonadism was made in these six subjects on the basis of their inadequate sexual and delayed epiphyseal maturation, immature but otherwise normal gonads, and impaired gonadotropin secretion. Although none of these subjects showed the sustained rise in serum FSH and LH concentrations characteristic of normal puberty,16-18 each did on occasion demonstrate serum levels of one or other gonadotropin within the normal adult range, as has been observed previously.18 Serum testosterone and estradiol concentrations were in the range seen in agonadal subjects, with the exception of occasional measurable serum estradiol values in M, who showed spontaneous breast development at age 29. Since her serum FSH and LH levels were not higher than those of the other, sexually infantile, subjects, it seems likely that this evidence of minimal ovarian estrogen secretion in M is the result of prolonged exposure to fluctuating and occasionally normal serum gonadotropin concentrations.

The horizontal distribution of affected members in these and previously reported pedigrees,1-4 together with the report of consanguineous parental mating in one family,4 suggest an autosomal recessive mode of inheritance for this form of hypogonadotropic hypogonadism. It is likely that this syndrome is distinct from Kallmann's syndrome, since hyposmia was not detected. Unfortunately, olfactory testing of unaffected relatives was not possible; recently Santen and Paulsen14 have suggested that hypogonadism and hyposmia may appear with varying expressivity in kindreds with Kallman's syndrome.

The only consistent endocrine defect observed in these patients was their lack of normal pubertal development, although four subjects in family A did show a possible impairment of ACTH/cortisol release during hypoglycemia. Deficient growth hormone release not associated with dwarfism has been reported in some hypogonadotropic patients;11 in our cases the growth hormone levels reached after insulin hypoglycemia were similar to those seen in normal children (greater than 5 ng/ml), but less than those usually seen in adolescents and adults (≥10 ng/100 ml). Improved growth hormone secretion in hypogonadotropic

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**Table II—Effect of conjugated estrogen on FSH and LH responses to LH-RH**

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<tr>
<th>Subject</th>
<th>LH-RH dose (µg)</th>
<th>Estrogen</th>
<th>0</th>
<th>15</th>
<th>30</th>
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</tr>
<tr>
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<td>&lt;2.0</td>
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*Premarin 1.25 mg daily for seven days.*
subjects following sex hormone replacement therapy has been reported. In adults clomiphene induces a rise in serum gonadotropin concentrations, presumably because of an antiestrogenic effect at the hypothalamic centres controlling the secretion of gonadotropin-releasing hormone(s). Sexually immature subjects, whether they be healthy children or hypogonadotropic eunuchs, do not as a rule respond. They do, however, respond to direct stimulation of the pituitary by LH-RH with a brisk rise in serum gonadotropin levels, which indicates that pituitary function is probably intact, and that the basic defect is at a hypothalamic or higher central nervous system level. For this reason the terms "hypothalamic or tertiary" hypogonadism have been suggested for cases such as these.

It seems clear that the LH-RH stimulation test can be used to differentiate pituitary from hypothalamic hypogonadism, although some variability in response of both FSH and LH is to be expected. One factor which clearly suppresses the pituitary response to exogenous LH-RH is pre-treatment with estrogen; small amounts of circulating estrogen may enhance the response, as is seen during the late follicular phase of the normal menstrual cycle.

References