CASE REPORT

Early postnatal treatment of hypogonadotropic hypogonadism with recombinant human FSH and LH

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Abstract

Background: Patients with hypogonadotropic hypogonadism may be diagnosed shortly after birth because of micropenis and cryptorchidism, combined with subnormal LH and FSH concentrations during the postnatal period.

Objective: To investigate whether treating these patients with gonadotropins postnataally, to mimic the physiological development, would improve testicular growth and fertility potential later in life.

Design: Our patient presented with micropenis. Serum hormone concentrations were measured monthly after delivery: LH and testosterone were undetectable, and FSH and inhibin B were below the normal range (0.05 – 0.17 IU/l and 79 – 112 pg/ml respectively).

Methods: From 7.9 to 13.7 months of age, the patient was treated with recombinant human LH and FSH in doses of 20 and 21.3 IU s.c. twice weekly respectively.

Results: During treatment concentrations of LH, FSH, inhibin B and estradiol increased to values within normal limits (0.7 – 1.88 IU/l, 0.17 – 3.24 IU/l, 121 – 268 pg/ml and 40 – 55 pmol/l respectively), whereas serum testosterone remained undetectable. Penile length increased from 1.6 to 2.4 cm and testicular volume, assessed by ultrasound, increased by 170%. No significant adverse events were observed.

Conclusions: Gonadotropin treatment in an infant with hypogonadotropic hypogonadism succeeded in inducing an increase in inhibin B and testicular growth.

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Introduction

Patients with hypogonadotropic hypogonadism may present at birth with symptoms of micropenis or mal-descended testes, or both. These boys lack the early postnatal surge in reproductive hormones that is normally seen in healthy boys – a feature that can be used for early establishment of the diagnosis (1, 2).

In addition to androgen replacement therapy during puberty and adulthood, fertility is becoming an increasingly important aspect of patient care, as possibilities of treating male infertility improve. To date, mainly adolescents and adult patients have been treated with monotherapy or combinations of human chorionic gonadotrophin (hCG), human MG and follicle-stimulating hormone (FSH) (3 – 7). Results depend on pre-treatment testicular size and whether or not there has been cryptorchidism. Prepubertal treatment with recombinant FSH stimulates inhibin B production and testicular growth (8).

Gonadotropins and androgens have a role in Leydig cell proliferation and germ cell differentiation early postnataally (9). Thus treatment of hypogonadotropic hypogonadism with gonadotropins during the postnatal period, when spontaneous production of reproductive hormones is high in healthy boys, may induce testicular growth and thereby improve future fertility potential. We present the first results of recombinant gonadotropin treatment in a boy with hypogonadotropic hypogonadism.

Case report

Patient

This was the third child of consanguinous Turkish parents. There was a family history of pes equinovarus and congenital heart disease, but no reproductive disorders. The patient was referred at the age of 2 weeks because of micropenis (1.6 cm stretched length). Both testes were fully descended and the scrotum well developed. The karyotype was 46,XY. Monthly measurements of spontaneous serum concentrations of reproductive hormones over 6 months revealed a total
lack of luteinizing hormone (LH) and testosterone. FSH and inhibin B were persistently below the normal range for his age (10) (Table 1). hCG stimulation with 100 IU/kg (single dose) increased serum testosterone to 5.7 nmol/l. All other pituitary axes were found to be normal. Thus the diagnosis of hypogonadotropic hypogonadism was established. Psychomotor development during follow-up until 1.5 years has been normal.

**Treatment**

At the age of 7.9 months, the child began treatment with recombinant human LH and FSH (treatment schedule outlined in the Table 1) after an initial kinetic study with s.c. injection of 20 IU LH and 2.5 IU/kg FSH (total dose: 21.3 IU). The dose of LH was doubled at 9.6 months. At the age of 12.2 months, testosterone suppositories were administered to improve penile growth further, and LH treatment was stopped. FSH injections were suspended at 13.7 months. The injections were given by a pediatric nurse as separate injections for LH and FSH, alternating between right and left thigh and gluteal region. The treatment was generally well tolerated and compliance excellent. No serious adverse events were encountered. There was recurrent otitis media throughout the treatment period, sleep disturbances between weeks 2 and 5 of treatment, intermittent nausea, and a local rash once at the injection site, which resolved spontaneously. Body hair and pigmentation increased slightly in amount during treatment. Control blood samples (hematology, liver and kidney function, coagulation status, thyroid hormones, insulin-like growth factor (IGF)-I and IGF-I binding protein-3) remained normal.

**Drugs**

Recombinant human LH and FSH (Luveris 37.5 IU and Gonal-F 37.5 IU) were obtained from Ares Serono, Geneva, Switzerland. Before injection, LH was dissolved in 0.5 ml solvent, and FSH in 1 ml solvent. Testosterone suppositories (1 mg) were manufactured by the hospital’s pharmacy, using a modification of the method of Hamburger & Pedersen-Bjergaard (11). This treatment is an effective alternative to peroral and injection therapy for androgen replacement (12).

**Assays**

Serum LH, FSH and sex hormone binding globulin (SHBG) were measured by time-resolved immunofluorometric assays (Delfia, Wallac Inc., Turku, Finland). Detection limits were 0.06 IU/L, 0.05 IU/L and 0.23 nmol/l respectively. Intra- and interassay coefficients of variation were less than 8% for LH and FSH, and 5% for SHBG. Serum testosterone was measured by RIA (Coat-a-Count, Diagnostic Products Corp., Los Angeles, CA, USA) with a detection limit of 0.23 nmol/l and intra- and interassay coefficients of variation less than 10%. Serum inhibin B was measured by specific ELISA (13) with a detection limit of 20 pg/ml, the intra- and interassay coefficients of variation were 15% and 18% respectively. Serum estradiol was determined by RIA (Pantex, Santa Monica, CA, USA) with a detection limit of 18 pmol/l and intra- and interassay coefficients of variation less than 8% and 13% respectively.

**Ultrasound**

Testis volume was determined with ultrasound (Aloka Micrus, Tokyo, Japan, linear transducer 7.5 MHz), and calculated as the mean volume of the left and right sides (14).

**Normal values**

Measurements were compared with age-specific longitudinal values for healthy boys (10), normal 95% ranges at 3 months being: testosterone 0.43–7.71 nmol/l, inhibin B 193–563 pg/ml, FSH 0.86–2.52 IU/l, LH 0.65–2.69 IU/l, estradiol 18.0–44.4 pmol/l.

**Table 1** Treatment schedule and serum concentrations of reproductive hormones (minimum and maximum values) during treatment of an infant with hypogonadotropic hypogonadism with recombinant human LH and FSH and testosterone suppositories. In treatment period 3, only one sample was available. Blood samples were taken before, and 4 and 6 h after injection.

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>0–7.9</td>
<td>7.9–9.6</td>
<td>9.6–11.3</td>
<td>12.2–13.7</td>
</tr>
<tr>
<td>Total LH dose (IU/2/week)</td>
<td>20</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FSH dose (IU/2/week)</td>
<td>21.3</td>
<td></td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>Testosterone suppositories (mg/day)</td>
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<td>n.d.</td>
<td>1</td>
<td>n.d.</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>n.d.</td>
<td>0.7–0.89</td>
<td>1.3–1.88</td>
<td>n.d.</td>
</tr>
<tr>
<td>LH (IU/l)</td>
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<td>0.17–2.12</td>
<td>1.26–3.24</td>
<td>0.88</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>123–169</td>
<td>150–176</td>
<td>125–150</td>
<td>153</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>25–27</td>
<td>40</td>
<td>55</td>
<td>26</td>
</tr>
<tr>
<td>Estradiol (pmol/l)</td>
<td>n.d.</td>
<td></td>
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</table>

n.d. = not detectable.
Ethics

The treatment was commenced after written consent from both parents, consent from the local Ethics Committee (07-00-013/00) and permission from the Danish Ministry of Health (2512-8928, 2512-10089).

Results

A single injection of 20 IU LH and 21.3 IU FSH s.c. increased serum LH and FSH to within normal limits (Fig. 1).

Results of serum measurements of reproductive hormones (minimum and maximum values) before and during the different treatment periods are shown in Table 1. LH and FSH increased to values within the low- and high-normal ranges respectively. Testosterone remained unmeasurable throughout the period, until testosterone suppositories were added to the treatment. Estradiol values increased to the high-normal range. After doubling of the dose of LH, an increased value was measured once. No gynecomastia developed. SHBG measurements remained unaltered. Serum inhibin B concentrations increased to approximately double the basal value during treatment with FSH and LH (Fig. 2). Addition of testosterone in period 3 caused a further increase.

The increase in serum inhibin B was parallel to the increase in testicular volume, as determined by ultrasound (Fig. 2). Testicular volume decreased from 59 mm$^3$ at birth to 31 mm$^3$ at 7 months of age. After 5 months of LH and FSH treatment, testicular volume had increased to 84 mm$^3$ (+170%). During LH and FSH treatment and before the start of testosterone treatment, stretched penile length increased from 1.6 cm to 2.4 cm. After supplementary treatment with testosterone, penile length was 2.7 cm.

During LH and FSH treatment, the standard deviation score for body height remained constant at $\pm$1.0, and bone age was equivalent to chronological age at 14 months. The weight-for-height percentile remained constant, at 60–65.

Discussion

This is, to our knowledge, the first report of a patient with hypogonadotropic hypogonadism treated with recombinant human LH and FSH during the first year of life. The treatment was successful in inducing testicular growth and, to some extent, in improving penile length. However, testosterone was also needed to achieve sufficient phallic growth.

Healthy boys have a significant increase in spontaneous production of reproductive hormones in the early period after birth (15–17). Animal studies and human observations suggest that this postnatal surge is important for genital growth and, potentially, also for functional development of the gonads (9, 18–20). There is evidence for a role of gonadotropins and androgens, not only during puberty but also postnatally, for Leydig cell proliferation and germ cell differentiation (9–21). Sertoli cell numbers increase in the first 3 months of life (22) and again during puberty, and the total number achieved is predictive of future spermogenic potential. In prepuberty, the testis consists mainly of seminiferous tubules, the length of which correlates with Sertoli cell numbers (23). Leydig cell volume increases around 3 months of age, probably under the influence of the LH surge (24). The increase in testosterone is probably initiated by LH. However, in culture, FSH also can induce testosterone response, potentially through paracrine mechanisms mediated by the Sertoli cells (24). Thus it seems rational to mimic the physiological development by replacing gonadotropins early in life. Such treatment has two goals: to treat the clinical symptoms of the patient during infancy and to improve the potential for achieving fertility.
The treatment doses applied here were derived empirically. The initial pharmacokinetic study in this patient indicated that the dosage was sufficient to augment LH and FSH to the normal range for 3-month-old boys. The results were comparable to those from studies in adult volunteers, showing a significant increase in serum concentrations of FSH and LH within 12 h and a more rapid decline of LH than of FSH (25).

Control blood samples showed persistently low LH and unmeasurable testosterone values throughout treatment. This may indicate that the half-life of LH was too short to maintain measurable values, or that the dose of LH was too low. In addition, the assay for testosterone does not have sufficient sensitivity to permit detection of very low serum concentrations. There were, however, clinical observations suggesting that there may have been a significant increase in intratesticular testosterone: penile length increased and body hair became more pronounced – both phenomena are androgen-dependent. Estradiol concentrations increased slightly, especially after doubling of the LH dose, which could indirectly reflect increased testosterone concentrations. However, the accuracy of the estradiol assay for very low concentrations is not good enough to exclude random fluctuation. Testicular growth was also observed, and may have been caused by direct FSH stimulation of Sertoli cell proliferation or intratesticular testosterone stimulation of the seminiferous epithelium, or both.

The fact that hCG injection in our patient lead to an increase in serum testosterone, whereas injection of LH did not, may indicate that the underlying genetic mechanism is an LH receptor mutation (26). However, low LH concentrations are not in agreement with LH resistance. We based the diagnosis in this patient exclusively on measurement of hormonal values (1, 2). Another genetic mechanism may be a mutation in the gonadotropin-releasing hormone receptor (27). However, these mutations are usually found only in cases of familial hypogonadotropic hypogonadism.

The dose of FSH was effective in increasing both FSH and inhibin B concentrations to within normal limits, and the addition of testosterone further increased inhibin B values. This may simply be due to a time-lag between start of treatment, when the testicles had not been stimulated for 8 months, and the achievement of a maximum response. It may, however, also indicate a synergistic effect of testosterone and FSH in stimulation of inhibin B production and secretion. In adults, inhibin B concentrations in serum are negatively correlated with serum FSH concentrations, but this feedback mechanism cannot be found in the first 2 years of life (10). Sertoli cells may be capable of an autonomous production of inhibin B, once they have been stimulated.

In conclusion, treatment of hypogonadotropic hypogonadism in one infant with recombinant human FSH and LH induced testicular and penile growth and augmented serum concentrations of inhibin B, thus succeeding in mimicking the physiological development that occurs early after birth. It remains to be seen whether early replacement with gonadotropins will be beneficial for the reduced fertility potential often seen in adult patients with hypogonadotropic hypogonadism despite hormonal treatment.

Acknowledgements

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References
