Upsala J Med Sci 89: 73–80, 1984

Induction of Male Puberty by Long-term Pulsatile Subcutaneous LH-RH Therapy

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ABSTRACT

Prolonged low dose LH-RH treatment was given to induce puberty in a 17.8-year-old male with hypogonadotrophic hypogonadism. The patient had developed panhypopituitarism after transcranial surgery of a craniopharyngeoma at the age of 16.8 years. One year after the operation he had no signs of pubertal development and was of short stature. A small portable automatically-timed infusion pump, connected to a subcutaneous (s.c.) catheter, was used for the 328-day-long treatment, which was given in periods of between 16 to 185 days. Twenty μg of LH-RH s.c. was given every 90 min. Growth hormone therapy, 8 IU intramuscularly (i.m.) twice weekly, was instituted at the same time.

During the prolonged LH-RH treatment the gonadotrophin secretion normalized. The serum concentration of testosterone increased to the normal range of adult males. Rapid pubertal progression occurred with development of pubic hair to adult type and increase in size of the penis. Testicular volume increased from 2 to 12 ml. Nocturnal emissions occurred after 30 weeks of pulsatile LH-RH treatment and sperms were found in the ejaculate after 43 weeks. The height of the patient increased from 162 to 176 cm. Thus, chronic pulsatile low dose LH-RH treatment can induce normal pituitary - gonadal function with pubertal maturation and spermatogenesis in primary male hypogonadotrophic hypogonadism.

INTRODUCTION

Nocturnal pulsatile release of luteinizing hormone (LH) is an early endocrine event during pubertal transition (1). In adults the gonadotrophin release is characterized by frequent pulses throughout both day and night, superimposed on a constant level of continous secretion (18). The episodic gonadotrophin secretion reflects intermittent LH-RH release from the hypothalamus (4,5).

In 1974 successful chronic intermittent high dose LH-RH treatment of male hypogonadism was reported (14). However, results of later studies with similar long-term treatment regimens in male hypogonadotrophic hypogonadism have been less successful (3,9,12,15). The increased knowledge of the hypothalamic neuroendocrinological regulation of the pituitary gonadotrophin secretion, brought forth by Knobil and co-workers (11), stimulated to new attempts at using LH-RH for treatment of hypogonadotrophic hypogonadism.

Prolonged pulsatile low dose LH-RH therapy has recently been used for successful treatment of male infertility due to secondary hypogonadotrophic hypogonadism (19). Here we report on pulsatile s.c. low dose LH-RH therapy for induction of puberty in a male with primary hypogonadotrophic hypogonadism of hypothalamic origin.

CASE REPORT

The patient was a 17.8-year-old Caucasian boy. Since the age of 11 he had complained of severe headache. At the age of 16.6 years he was referred to the Department of Paediatrics because of insufficient growth and lack of pubertal development. His height was 158 cm and penis and pubic hair development were classified according to Tanner (21) as stage 2 and 1, respectively. He also had symptoms indicating diabetes insipidus. Neuroradiological examination revealed a craniopharyngeoma. The tumour was surgically removed and postoperative radiotherapy (50 Gy) was given. After the treatment the patient developed panhypopituitarism and was substituted with DDAVP (Minirin®, Ferring), cortisone acetate (Cortone®, MSD) and levothyroxine (Levaxin®, Nyegaard).

One year after the operation, at the age of 17.8 years, he was still of short stature, 162 cm, and had no signs of pubertal development. Penis was in Tanner stage 2, pubic hair in Tanner stage 1 and the testicular size was 2 ml. He had no axillary hair or lowering of the voice. His bone age was 11 years (8).

The serum levels of gonadotrophins were very low: follicle-stimulating hormone (FSH) 0.25 µg/l and LH 0.17 µg/l (normal range for men; FSH: 0.5 - 3.0 µg/l, LH: 0.4 - 3.0 µg/l) (22). The acute gonadotrophin response to LH-RH stimulation (100 µg intravenously, i.v.) was very low. The serum prolactin level (18 µg/l) was at the upper part of the normal range (<20 µg/l). The serum level of testosterone was prepubertal, 0.14 nmol/l (normal range for men: 10 - 45 nmol/l.)

HORMONE ASSAY METHODS

FSH and LH were measured by a radioimmunosorbent technique with indirectly coupled antibodies (23). The results were expressed in micrograms per liter using highly purified FSH and LH preparations as reference standards (16,17). One microgram of the FSH preparation was equivalent to 369 μg of the LER-907 in the FSH immunoassay and 1 μg of LH was equivalent to 84 μg of LER-907 in the LH immunoassay. Prolactin in serum was measured with a similar radioimmunoassay technique using particulate immunosorbents (22).Testosterone in serum was determined with a radioimmunoassay using an antiserum to testosterone-3-oxime-BSA conjugate (6).

TREATMENT

Long-term pulsatile LH-RH therapy was given by means of a small portable, automatically-timed infusion pump (Zyklomat®, Ferring, Kiel, FRG). The treatment was given for periods of between 16 to 185 days (total treatment length 328 days) interrupted by periods without therapy of between 17 to 85 days. The pump was connected to a chronic indwelling catheter, which was inserted in the subcutaneous fat tissue of the lower abdominal wall during the first 148 treatment days. Local irritation at the catheter site then occurred and the subcutaneous insertion was changed to the ventral part of the upper thigh. The catheter was changed approximately once every month. The pump infused 50 μl of the LH-RH solution during one min once every 90 min. The concentration of the LH-RH solution was 20 μg/50 μl.

Growth hormone treatment (8 IU Crescormon® i.m., KabiVitrum, twice a week)was initiated together with the pulsatile LH-RH therapy . The treatment was monitored by clinical examinations including estimations of Tanner stage of penis and pubic hair development and measurements of testicular volume. Peripheral venous blood samples were frequently drawn for radioimmunological estimations of serum concentrations of FSH, LH, prolactin and testosterone.

RESULTS

Serum concentrations of FSH, LH and testosterone during the first four treatment periods (18, 16, 29 and 40 days, respectively) of s.c. pulsatile administration of 20 μg LH-RH every 90 min are shown in Fig. 1. Within 10 days of pulsatile LH-RH therapy both FSH and LH concentrations in serum had increased to the lower normal range for men. The gonadotrophin rise was accompanied by an increase of the serum testosterone level up to 5 nmol/l at the end of the first treatment period. The serum concentrations of gonado-

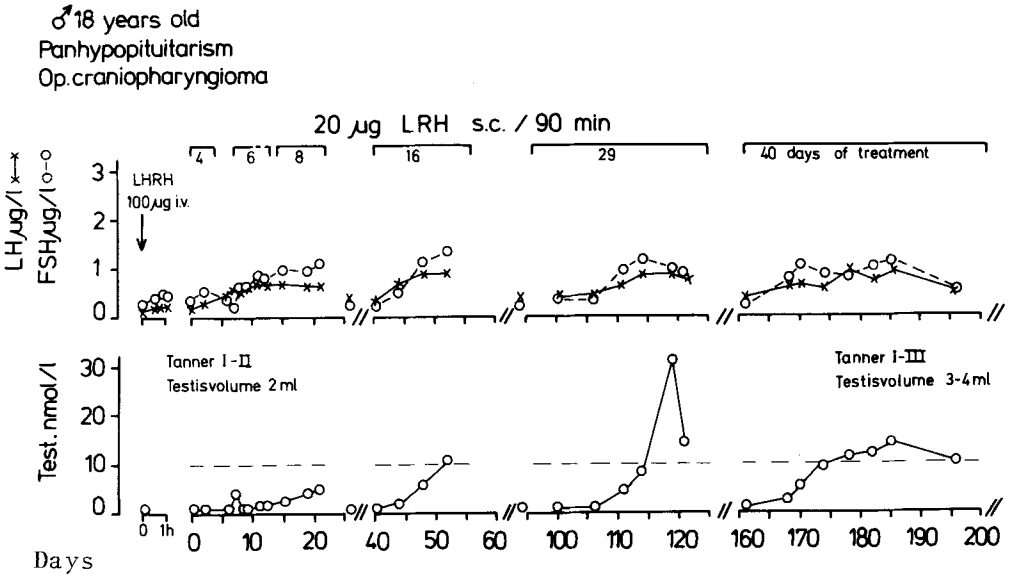

Figure 1. Serum concentrations of FSH, LH and testosterone in an 18-year-old male with primary hypogonadotrophic hypogonadism during 103 (18,16,29 and 40) days of pulsatile subcutaneous low dose LH-RH therapy.

trophins and testosterone decreased to pretreatment levels when the pulsatile LH-RH administration was interrupted. The gonadotrophin secretion increased rapidly during the next treatment period and the serum testosterone concentration reached the lower limit of the normal range for men after 12 days. During the next two treatment periods of pulsatile LH-RH therapy there was a similar increase of the serum gonadotrophin concentrations and the serum testosterone level rose to the normal range for adult men.

The serum concentrations of FSH and LH remained within the normal range during the 185-day-long fifth treatment period (Fig. 2). The testosterone level increased rapidly to the lower part of the normal range but then decreased after 30 days of treatment. Local irritation at the catheter site occurred at the same time and the place of catheter insertion was changed to the ventral part of the upper thigh. This was followed by a normalization of the serum testosterone level, which varied between 22 and 34 nmol/l during the remainder of the treatment period. When the pulsatile LH-RH therapy was interrupted, the gonadotrophin and testosterone concentrations decreased to pretreatment serum levels. A rapid normalization of the hormone concentrations occurred when the therapy was reinitiated 85 days later. The serum

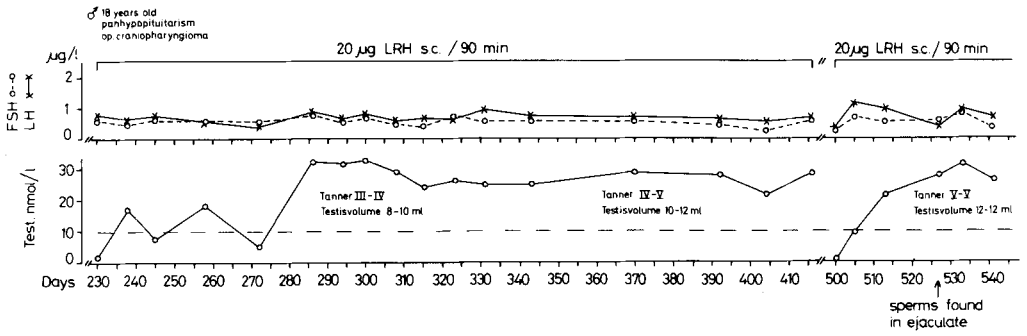

Figure 2. Serum concentrations of FSH, LH and testosterone in an 18-year-old male with primary hypogonadotrophic hypogonadism during 225 (185 and 40) days of pulsatile s.c. low dose LH-RH therapy.

was normal during the whole treatment period. A decrease to pretreatment serum levels of both gonadotrophin and testosterone concentrations occurred.

A summary of the somatic growth and the pubertal development of the patient during combined pulsatile LH-RH and growth hormone treatment is given in Table 1. He increased 14 cm in height and gained 21.4 kg in weight, little of which was adipose tissue. After 35 weeks his bone age had increased from 11 to 14 years. The genital development was rapid and the penis and pubic hair were classified as Tanner stage 5 after 35 and 47 weeks, respectively, of pulsatile LH-RH treatment. The testicular volume increased 10 ml (from 2 to 12 ml). Slight gynaecomastia, breast tenderness as well as early-morning erections appeared from the 14th week of therapy. Nocturnal emissions occurred after 30 weeks. The first ejaculate for sperm analysis was obtained after 43 weeks of pulsatile LH-RH therapy. It contained mobile sperms. After another 4 weeks of LH-RH treatment the concentration of sperms in the ejaculate was 2×10^6 /ml.

DISCUSSION

This study shows that prolonged pulsatile s.c. administration of low dose LH-RH is an effective and safe therapy for pubertal induction and maturation in primary male hypogonadism due to hypothalamic-pituitary failure. Our report confirms two recently published studies on induction of male puberty by LH-RH (7,10).

	April 82	Oct 82	Jan 83	May 83	Sept 83
Height (cm)	162	164.5	169	172.5	176
Weight (kg)	47.6	51	55	61.5	69
Penis (Tanner stage)	2	2-3	4	5	5
Pubic hair (Tanner stage)	1	1	3	4	5
Testis volume (ml; left/right)	2/2	3/4	8/10	10/12	12/12
Bone age (years, G-P)	11			14	

Table 1. Pubertal development and growth in an 18-year-old male with primary hypogonadotrophic hypogonadism after 328 days of pulsatile LHRH treatment given during 17 months of growth hormone therapy.

The dose of 20 μg LH-RH s.c. every 90 min induced a rapid increase of the pituitary secretion of both FSH and LH. The serum gonadotrophin concentrations remained within the normal range during the treatment periods. The normalization of the gonadotrophin secretion during the LH-RH treatment stimulated gonadal activity to prompt testosterone secretion and testicular growth. Maturation of spermatogenesis, which normally occurs in late puberty (13), was evident after 43 weeks of LH-RH treatment of our patient.

The somatic pubertal development was rapid. Typical events of early normal puberty such as gynaecomastia and early-morning erections occurred within 4 months of pulsatile LH-RH therapy. Complete pubertal change was obtained after 47 weeks of treatment. This is very rapid in comparison with normal pubertal development which takes about 3.5 years (20). The bone age increase in our patient was also accelerated, 3 years in 35 weeks.

The subcutaneous pulsatile LH-RH therapy was well accepted by the patient. The treatment was interrupted over various periods for psychological reasons and school holidays. The subcutaneous route of administration proved to be safe. The only complication was a short period of local irritation at the catheter site. The insertion site was then changed from the lower abdominal wall to the ventral part of the upper thigh. The subcutaneous absorption of

LH-RH in the thigh does not seem to be inferior to that of the lower abdominal wall, as indicated by maintained normal serum concentrations of gonadotrophins and testosterone.

ACKNOWLEDGMENTS

This study was supported by a grant from the Swedish Medical Research Council (grant No. 13X-3145). We are indebted to Ferring AB, Sweden, for generous supply of infusion pumps and LH-RH and to Mrs K. Mattsson for secretarial assistance. We thank the technical staff of the Hormonal Laboratory of the Department of Clinical Chemistry and the Primate Laboratory of Reproductive Research at the Department of Obstetrics and Gynaecology for their skilful assistance.

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