Successful Treatment of Dwarfism and Hypogonadism after Total Removal of Craniopharyngioma

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Abstract

A case of successful treatment of child craniopharyngioma is reported. The tumor was totally removed seven years ago and the patient's height became normalized by human growth hormone (HGH) therapy lasting for 2 1/2 years. Completed development of his sexual characteristics and induction of spermatogenesis resulted from a combination therapy with human chorionic gonadotropin (HCG) and human menopausal gonadotropin (HMG).

Key words: craniopharyngioma, total removal, dwarfism, HGH therapy, hypogonadism, HCG-HMG therapy

Introduction

The treatment for craniopharyngiomas is still controversial.^{4,6,8)} However, there has been an increasing number of reported cases with long survival after extensive removal of the tumor and other multimodal therapies.^{7,10)} Further problems afflicting such children are dwarfism^{1,16)} and hypogonadism,¹¹⁾ which are almost always accompanied with craniopharyngioma.

We are reporting a successful case, with completed development of all sexual characteristics and induction of spermatogenesis by gonadotropin treatment, whose tumor was totally removed 7 years ago and his height became normalized as a result of human growth hormone (HGH) therapy lasting for 2 and a half years.

Case Report

The patient, a 13-year-old boy was admitted because of his short stature, nausea and vomiting on September 11, 1972. His short stature was noticed at the time of his entrance to elementary school in 1966. He experienced attacks of headache once or twice a month and had noticed a gradual loss of his visual acuity, which required him to wear glasses since 1970. Three months before admission, his headaches in-

creased in severity and frequency (three times a week) and were sometimes accompanied with vomiting.

On admission, his height was 130.3 cm and his weight 28.3 kg. His sensorium was slightly lethargic. His temperature did not rise above 35.5°C. His visual acuity was corrected to the normal range by glasses. Mild papilledema was found by fundoscopy. Plain craniogram showed suprasellar calcification (Fig. 1) and his bone age was estimated as that of a 10-year-old boy. Carotid angiography revealed an elevated A₁ portion and unrolling of the anterior cerebral artery. An air study showed filling defects of the anterior third ventricle and the chiasmatic cistern. Hormone assay revealed low or no response of the GH to the insulin tolerance test and arginine test. Serum FSH and LH were low and did not respond to LH-RH. Serum TSH and plasma ACTH were in the subnormal range. There was no diabetes insipidus. Blood picture and serum chemical studies were within normal range.

The patient was referred to our department for treatment of the suprasellar mass. Right fronto-temporal craniotomy was performed on December 4, 1972. The cystic mass was totally removed through the subfrontal approach. The pituitary stalk was sacrificed because of tumor invasion. The pathological diagnosis was adamantinomatous craniopharyngioma. The postoperative course was uneventful except for mild diabetes insipidus, which was controlled by antidiuretics. The patient was discharg-

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Fig. 1 Plain skull film on admission showing irregular calcification at suprasellar region and no sellar enlargement.

ed on February 4, 1973 with hormone replacement therapy with steroid (Hydrocortone; 20 mg/day), thyroid hormone (Thyradine S; 100 μ /day) and antidiuretics (Fruitran; 2 mg/day and Diabinese; 100 mg/day). No other treatment was given until March, 1975, when he was chosen as a candidate for the use of HGH for secondary dwarfism. He was 15 years old and his height at that time was 143.5 cm (below -2 SD of the mean growth curve for Japanese boys). He was given 8 units of HGH (Crescormone) a week for 2 years and 4 months. At this time HGH treatment was terminated, because his height reached 156.6 cm. There was a further, natural increase in his height of 7.2 cm in 2 years and 8 months, and when he was 19 years old his height reached 163.8 cm (Fig. 2).

Because the patient showed no secondary sexual characteristics and there was no evidence of tumor recurrence according to CT scan (Fig. 3), gonadotropin treatment was started in March, 1980 for his hypogonadism. At this time, his serum testosterone level was 0.2 ng/ml, and serum LH and FSH peak levels to LH-RH test were 5.0 and 2.0 mIU./ml, respectively (Table 1). This treatment consisted of two steps; first, 3,000 units of human chorionic

Fig. 2 Height curve before, during and after HGH treatment. Patient's height at different times is plotted on the mean height curve of normal Japanese boys. The height became normalized after total removal of tumor followed by HGH treatment. Gonadotropin therapy was initiated when patient's height reached 163.8 cm.

Fig. 3 CT scan before gonadotropin treatment showing no suprasellar mass nor tumor calcification.

gonadotropin (HCG, Pregnine) were given intramuscularly three times a week. After induction of secondary sexual characteristics for a year, 75 units of human menopausal gonadotropin (HMG, Humegone) were given three times a week for 9 months in addition to HCG. After 6 months, another HMG regimen was given until March, 1983. The effectiveness of this treatment has been judged by the following parameters (Table 1); the secondary sexual characteristics were evaluated by the volume of the testis (orchidometry), length and diameter of the

Table 1 HCG-HMG treatment for hypogonadism in craniopharyngioma*

	1980. 3	9	1981. 1	3	4	6	1982. 1	2	7
Penis									
Length (cm)	3.2	4	4	4.5		6	6.3	6.5	6
Circum. (cm)				2.3		8	7.3	8	7.9
Testis (ml)	2	3	4	4	5	6-8	8	6, 5	5
Hair									
Pubic	—	—	I°	II°		II-III°	IV°		IV°
Armpit	—	—	—			±	I°		II°
Erection	—	—		±	+		++		
Ejaculation	—	—		—			—		
Change of voice	—	—	—	—	+				+
Testosterone (ng/ml)	0.2	1.53		9.52		8.25		9.8	6.7
LH (mI.U./ml)	5.0	3.0							
FSH (mI.U./ml)	2.0	2.0							
Body height (cm)	163.8	164.3		166		168		169.1	

*The effectiveness of gonadotropin treatment has been judged by the changes of secondary sexual characteristics, periodic hormone assay and biopsy of testicular gland.

penis, maturation of the pubic or armpit hair (Tanner's grading). Hormone assays were made for serum testosterone, LH and FSH. Spermatogenesis and maturation of testicular glands were assessed by biopsy of the testis.

Although the secondary sexual characteristics had been completely absent at the initiation of this treatment (Fig. 4A), the pubic hair, volume of testis, the size of penis increased during a year of HCG treatment and just before the HMG treatment. By the combination of HCG and HMG treatments for 9 months, further maturation of the sexual characteristics such as erection of the penis and change of voice took place. The serum testosterone level became normalized within a month of HMG treatment and was maintained at a normal level thereafter. The completion of secondary sexual characteristics has been achieved during the second administration of HMG treatment (Fig. 4B). A biopsy of the testis before treatment showed an immature narrow tubular structure without identifiable Sertoli and Leydig cells (Fig. 4C). After the treatment, considerable increases in the tubular diameter, maturation of the germinal cell content, such as Sertoli cells and gonocytes and matured fibrillary matrix with Leydig cells have been demonstrated (Fig. 4D). Spermatogenesis has now been initiated by the maturation of the testis.

This patient is now 24 years old, working as a businessman and living a useful life.

Discussion

The effectiveness of HGH treatment for primary pituitary dwarfism has been established and more than 90% of the cases have been successfully treated.¹⁶⁾ However, there have been a few reports on the effectiveness of HGH for secondary dwarfism, due to craniopharyngioma^{1,16)} or other intracranial tumors.¹⁶⁾ Since 1975, we have been using HGH in eleven cases whose tumors had been controlled by various treatments for a long time and yet who satisfied the following diagnostic criteria proposed by the study group of pituitary dwarfism in Japan: 1) a height below -2 SD of the mean height curve, 2) a growing rate of less than 4 cm per year, 3) before closure of the epiphyseal line and a bone age of less than 75% of the chronological age, 4) loss or diminished secretion of HGH. As a result of HGH therapy, all except one showed an increased annual growth rate that was twice that of the pretreatment value. However, there are some problems regarding HGH treatment for craniopharyngioma patients.²⁾ There is a tendency of a decreasing annual growth ratio as the duration of the treatment is prolonged. This may be due to HGH antibody formation.³⁾ Other factors influencing the results are shortage of dosis,⁹⁾ effect of steroids¹⁴⁾ used simultaneously and the possibility of tumor regrowth.

The replacement therapy for gonadal hormones has been more complicated and difficult. Testosterone or LH-RH had been used for these purposes,

Fig. 4 Maturation of sexual organs by gonadotropin therapy. A: Before gonadotropin treatment (at age of 19), no secondary sexual characteristics were found regarding the size of penis, volume of testis and pubic hair. B: The second sexual characteristics were completed by HCG-HMG therapy. C: Biopsy of the testis shows immature tubular structures and no Sertoli cells nor Leydig cells were identified before treatment. D: After HCG-HMG treatment, increase in the tubular diameter and maturation of germinal cell contents are found. Evidence of early spermatogenesis became manifested.

but the results were not satisfactory.^{9,13} HCG-HMG therapy has been developed for the treatment of hypogonadotropic hypogonadistic males^{5,15} and fewer numbers of successful cases have been reported in the primary or secondary conditions.¹¹⁻¹³ The rationale of this treatment is to stimulate the Sertoli cells by HCG, which has LH effects to induce secretion of testosterone, and then to achieve spermatogenesis by HMG, which has FSH effects.^{5,9,15} It is not easy to evaluate whether this regimen is the best for hypogonadism of craniopharyngioma. Lytton and Kase¹¹ reported a case of a eunuchoid male with craniopharyngioma whose testicular size increased and who had an early stage of spermatogenesis induced by HCG-HMG treatment. Johnsen⁵ and Steinberger¹⁵ stated separately that a combined therapy with HCG and HMG is necessary for spermatogenesis in hypogonadotropic hypogonad-

ism. This is the first adolescent case of a successful completion of secondary sexual characteristics and induction of spermatogenesis by HCG-HMG therapy after the total removal of craniopharyngioma and restoration of normal height by HGH treatment.

It has to be established in the future whether any maintenance regimen is necessary after the induction of spermatogenesis or if there is any safe and possible treatment for female hypogonadism. We hope that an ever-increasing number of cases with craniopharyngioma will benefit from these multimodal therapies.

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