A Super Long-Acting LH-RH Analogue Induces Regression of Hypothalamic Hamartoma Associated with Precocious Puberty


Department of Neurosurgery, Nagoya University School of Medicine, Nagoya, Japan

Summary

We treated a 1-year-old female with a hypothalamic hamartoma and precocious puberty with leuprolide acetate depot, a super long-acting hormone-releasing hormone analogue (Tap-144-SR; [D-Leu⁶-[des-Gly¹⁰,NH₂]₁]-LH-RH ethylamide acetate). The infant’s major symptoms were genital bleeding and gynaecomastia. The LH-RH analogue (30 μg/kg) was injected subcutaneously once every 4 weeks. Clinical and laboratory manifestations of precocious puberty showed marked improvement. A follow-up after 16 months of treatment, the size of the tumour decreased significantly and remained unchanged for 2 years of further follow-up. To the best of our knowledge, this is the first hypothalamic hamartoma case in whom a decrease of tumour size under treatment with LH-RH analogue has been documented. But, because diagnosis of hamartoma is only based on neuroradiological and not on histological examinations, the possibility of a gangliocytoma cannot be excluded with certainty.

Keywords: Hypothalamic hamartoma; precocious puberty; LH-RH analogue.

Introduction

Hypothalamic hamartoma with central precocious puberty is relatively rare. A survey of 281 cases of central precocious puberty in Japan identified only 39 cases (14%) related to hypothalamic hamartoma [9]. The pathogenesis of precocious puberty and its optimal treatment have not been established. There are two theories on the pathogenesis of precocious puberty: the production of LH-RH in tumour tissue and the destruction of the inhibitory mechanism of the sex centre [20].

Current therapeutic options include the surgical extirpation of the hamartoma [1, 4–6, 10–12, 14–18, 21, 22, 29, 31, 32] and the administration of hormone therapy with an LH-RH analogue [2, 3, 7–9, 13, 22–24, 27, 28, 32].

In the present study, we treated a patient with precocious puberty with subcutaneous injections of a long-acting LH-RH analogue.

Case Report

Genital bleeding occurring at 1 to 3 month intervals developed in a 1-month-old Japanese female who had been a full-term infant (40 weeks), with no abnormal findings at birth. Bilateral gynaecomastia was observed 2 months later, and her parents then consulted a local physician.

At that time her height was 88 cm (+ 2.5 SD) and her weight was 14.5 kg (+ 3.7 SD). A plain X-ray of the hand revealed that her bone age, estimated by the method of Greulich and Pyle was that of a 5 to 6-year-old child. Results of laboratory tests were within normal limits. Levels of LH, FSH and oestradiol were 2.3 mIU/ml, 6.6 mIU/ml, 10.0 pg/ml, respectively. CT and MRI showed a suprasellar lesion. The infant was referred to the Department of Neurosurgery, Nagoya University School of Medicine. Her height and weight at the time of referral were 90 cm and 16.5 kg, respectively. She had grade II according to Tanner’s classification, and she exhibited grade I pubic hair. Her visual acuity, visual field and mental development were all normal.

Hormonal assays showed no marked abnormalities in the baseline LH, FSH and oestradiol levels. However, an LH-RH stimulation test using intravenous injection of 0.44 mg LH-RH showed hyperresponsiveness of LH and FSH. The former increased up to 73.9 mIU/ml at 30 min and the latter to 14.0 mIU/ml at 60 min (Fig. 1).

The serum level of α-fetoprotein was 3 ng/ml (normal range 0 to 20 ng/ml) and the serum level of β-HCG was 0.2 ng/ml (normal range 0 to 0.5 ng/ml). Cytological examination of the vaginal mucosa showed no malignancy, but hyperoestrogenic features were present. The infant exhibited no convulsions or laughing attacks, and was not mentally retarded.

A T1-weighted MRI showed a well demarcated 15 mm iso-intense mass in the central part of the suprasellar region. This mass...
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Fig. 1. Serum levels of LH (upper) and FSH (lower) in the presence of LH-RH stimulation and before and after treatment with an LH-RH analogue.

Fig. 2. An MRI showed a mass in the hypothalamic region. (A) T1-weighted axial image before treatment. (B) T1-weighted sagittal image with Gd-DTPA before treatment with LH-RH analogue. (C) T1-weighted axial image after treatment. (D) T1-weighted sagittal image after treatment.

Discussion

Hypothalamic hamartoma associated with precocious puberty is treated by either surgical removal of hamartoma or hormonal therapy. Although the mortality rate associated with surgical treatment has decreased with recent microsurgical operation, the efficacy of surgical removal of hamartoma has not been established. Hypothalamic hamartomas are anomalous and are difficult to remove completely because of the tight adhesion between the lesion and the hypothalamus and it has been reported to be associated with some complication, such as the risk of inducing diabetes insipidus, oculomotor palsy, hemiparesis, and acute brain swelling [1, 12, 16, 17, 31].

On the other hand, hormonal therapy with medroxyprogesterone acetate, cyproterone acetate, and LH-RH analogues has also been used for the treatment of central precocious puberty. Recently developed long-acting LH-RH agonist analogues, which initially stimulate and then inhibit the release of pituitary gonadotropins, provide excellent therapeutic results [7–9, 13, 22, 23, 27, 31]. Between 1979 and 1983, 24 out of 107 children with central precocious puberty had hypothalamic hamartomas and they were treated with the long-acting LH-RH analogue D-Trp<sup>6</sup>-Pro<sup>9</sup>-NEt-LH-RH in U.S. study [22]. This medication suppressed the levels of gonadotropin and sex steroids,