Original Article

An Infant Case of Hyperprolactinemia Induced by a Functional Disorder of the Hypothalamus

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Abstract. Although functional hyperprolactinemia originating in the hypothalamus has been observed, there have so far been few reports of this condition occurring in children. This report describes a 1-yr-and-4-mo old boy with hyperprolactinemia due to functional disorder of the hypothalamic region. He was referred to our hospital because of left gynecomastia which had been observed for one month. His left breast development was stage II, right breast stage I, and pubic hair stage I by Tanner stages, and his bilateral testicular volume was 1 ml. Both his height and growth velocity were normal and his bone age was not advanced. The basal PRL level was high (40.4 ng/ml), but other sex steroids and adrenal androgen levels were normal. GnRH demonstrated the prepubertal stage. PRL response to TRH was normal and levodopa suppressed the increased basal PRL level. His chromosomal finding was 46, XY and macroprolactinemia was ruled out. Repeated MRI examinations did not demonstrate any organic lesions in the brain. He was diagnosed as having hyperprolactinemia induced by a functional disorder of the hypothalamus. His gynecomastia reduced and the high PRL level decreased without medication after 1 year.

Key words: functional hyperprolactinemia, hypothalamus, infant

Introduction

There are numerous causes of excessive secretion and release of PRL associated with increased blood levels. The hypothalamic secretion of a PRL-inhibiting factor (PIF) is believed to represent the principal mechanism regulating PRL release and dopamine is the most important inhibitory factor (1). Consequently, any interference with dopamine synthesis or transport from the hypothalamus may result in elevated prolactin levels. Although most hypothalamic disorders causing hyperprolactinemia are organic, functional disorders such as Chiari-Frommel syndrome (2) and Argonz-del Castillo syndrome (3), both of which are called idiopathic galactorrhea-amennorhea in adult females, exist. However, there are few reports of child cases with functional hyperprolactinemia (4). This report describes an infant case of functional hyperprolactinemia which seemed to have originated from a hypothalamic lesion.

Case Report

A 1-yr-and-4-mo old boy was referred to Okayama Medical Center because of left
gynecomastia. He had been delivered in the cephalic position without asphyxia at 34 wk of gestation. His birth weight was 2215 g, appropriate for his gestational age. He had developed normally, but his family members noticed a left breast bud 1 mo prior to presentation. He had not taken any specific medicine for an extended time period. Based on examinations the patient was not thought to have been affected by endocrine disrupting chemicals. His height was 80.0 cm (+ 0.48 SD), weight 9.7 kg (– 0.45 SD), and growth velocity 14.1 cm/year (+ 0.13 SD). He had no major anomalies and his proportions were normal. His left breast development was stage II, right breast stage I, and pubic hair stage I by the Tanner stages. His bilateral testicular volume was 1 ml. His bone age according to Greulich-Pyle was 1 yr and 3 mo (bone age/chronological age = 93.8%). No abnormalities of the chest or abdomen were found.

The patient’s complete blood count, routine serum chemistries and urinalysis were all within normal range. No abnormalities were observed in his hypothalamus and pituitary by magnetic resonance imaging (MRI). The results of endocrinological testing are shown in Table 1. The basal PRL level was determined by a chemiluminescence immunoassay (CLIA) using the ARCHITECT® analyzer i 2000 (ABBOTT JAPAN CO., LTD., Tokyo, Japan) and it was found to be high. E₂, other sex steroids, and adrenal androgen levels were all normal. Thyroid function was also normal. The results of a GnRH test indicated the prepubertal stage. TRH test demonstrated a normal PRL response (doubling of basal level) with increased basal concentration and normal TSH response. The levodopa test demonstrated a normal GH response, while the PRL level was suppressed. The patient’s karyotype was 46, XY. Macroprolactinemia, in which most circulating PRL forms large protein complexes and is a major cause of idiopathic hyperprolactinemia, was not demonstrated using polyethylene glycol (5) and protein G column (6) methods.

Table 1  Endocrinological data

| A: basal data         | DHEA-S: 27 ng/ml (normal range, 28-223) |
|-----------------------|-----------------------------------------|
| LH: 0.1 mIU/ml (normal range, <0.05–0.29) | ACTH: 40.2 pg/ml (normal range, 7.4–55.7) |
| FSH: 0.6 mIU/ml (normal range, <0.12–1.52) | free T₈: 1.32 ng/dl (normal range, 0.70–1.48) |
| PRL: 40.4 ng/ml (normal range, 3.6–12.8)   | TSH: 0.77 μIU/ml (normal range, 0.35–4.94) |
| hCG: <0.1 mIU/ml (normal range, <0.5)      |                                         |
| E₂: <10 pg/ml (normal range, <10)          |                                         |
| testosterone <0.05 ng/ml (normal range, 0.03–0.13) |                                         |

| B: provocation test |
|---------------------|
| \[\text{min}\]     | 0 | 30 | 60 | 90 | 120 |
|---------------------|---|----|----|----|-----|
| GnRH               | LH (mIU/ml) | 0.3 | 3.0 | 2.5 | 1.8 | 1.2 |
| FSH (mIU/ml)       | 0.8 | 2.9 | 3.5 | 3.0 | 2.7 |
| TRH                | PRL (ng/ml) | 21.2 | 42.4 | 34.0 | 24.4 | 20.0 |
| TSH (μIU/ml)       | 0.20 | 4.72 | 3.88 | 3.17 | 1.92 |
| Levodopa           | PRL (ng/ml) | 25.8 | 11.8 | 8.1 | 6.6 | 7.7 |
| GH (ng/ml)         | 2.3 | 19.9 | 14.6 | 5.7 | 2.3 |

hCG: human chorioic gonadotropin, DHEA-S: dehydroepiandrosterone sulfate.
Based on these observations, the patient was diagnosed as having hyperprolactinemia which was presumably induced by a functional disorder of the hypothalamus.

In the year following the patient’s first presentation, his gynecomastia improved gradually and the PRL level declined to a normal level (11.6 ng/ml) without medication.

**Discussion**

In contrast to the secretion of other pituitary hormones, the secretion of PRL tends to increase in the absence of hypothalamic influence. Dopamine, the most important PIF, is a secretory product of the tuberoinfundibular dopaminergic pathways and it is present in hypophyseal-portal vessel blood (7). Therefore, lesions within or in the vicinity of the hypothalamus may prevent the secretion or the transmission of this inhibitory factor (8). On the other hand, TRH which is one of the most important putative PRL-releasing factors directly stimulates the formation of lactotropes in the pituitary (9, 10).

In the present case, the basal PRL level was less than 100 ng/ml and TRH normally raised the basal PRL level more than two-fold. Pituitary adenoma, which is thought to account for half of all instances of hyperprolactinemia, is more likely to occur when the basal PRL level is greater than 100 ng/ml and the PRL response to TRH is subnormal (9, 10). Moreover, repeated observations by MRI did not find a pituitary tumor. Consequently, pituitary adenoma including microadenoma was excluded from the diagnosis.

Levodopa, which is converted to dopamine in peripheral tissues and the brain, suppressed the increased basal PRL level, suggesting that there was a lesion within or in the vicinity of the hypothalamus. Moreover, no organic lesion was observed by repeated MRI examinations of the hypothalamic region, either. The patient’s gynecomastia reduced and his PRL level decreased naturally. Taken together, the above findings suggest the hyperprolactinemia seen in this patient was likely caused by a dysfunction of the hypothalamus, though the exact reason for the dysfunction still remains unknown.

Functional hyperprolactinemia induced by a hypothalamic lesion such as Argonz-del Castillo syndrome and Chiari-Frommel syndrome, is sometimes the cause of galactorrhea-amennorhea syndrome in adult females. In Argonz-del Castillo syndrome, it is thought that the inhibited secretion of PIF is the cause of hyperprolactinemia and in Chiari-Frommel syndrome, it is thought that the secretory promotion of PRL by stimulation of the nipple is the cause of hyperprolactinemia when breastfeeding is continued. However, there have so far been no reports on hyperprolactinemia in the absence of demonstrable brain lesions in young patients in the literature. Cianfarani et al. reported 3 patients with hyperprolactinemia caused by hypothalamic dysfunction (4). These 3 patients had other symptoms of hypopituitarism such as diabetes insipidus and GH deficiency or hypothalamic osmoreceptor impairment, in addition to hyperprolactinemia. Among these 3 patients, one patient had focal swelling in the pituitary stalk at the first examination. In the second patient, the hypothalamic CT scan and MRI findings remained normal 3.5 yr after the first evaluation. In comparison to these patients, our patient showed only hyperprolactinemia and his symptoms disappeared. However, the third patient described by Cianfarani et al. showed a small lesion in the hypothalamus after a two-year follow-up. Therefore, careful clinical, endocrinological evaluations and neuroimaging are recommended for patients with hyperprolactinemia.

While PRL is not believed to play a direct role in gynecomastia in men, in instances of gynecomastia which are not caused by PRL secreting tumors, and in which the PRL level is elevated, the elevation may be a secondary
consequence of hyperestrogenemia (11). However, in our case, the E\textsubscript{2} level was normal and the gynecomastia improved as the PRL level decreased. On the other hand, the PRL level tends to be high in the neonatal period, and thereafter it gradually decreases until 3 mo of age after which a constant value tends to be observed until 1 yr of age. In our case, the PRL level 40.4 ng /ml at the age of 1 yr and 4 mo was extremely high and thereafter it decreased sharply to 11.6 ng/ml. We do not think this change was a physiological one. Thus, the causal relationship between the gynecomastia and hyperprolactinemia remains to be elucidated.

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