Prolactin Response to Thyrotropin-Releasing Hormone in Children with Gynecomastia, Premature Thelarche and Idiopathic Precocious Puberty

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ABE, K., MATSUURA, N., NOHARA, Y., FUJITA, H., FUJIEDA, K., KATO, T. and MIKAMI, Y. *Prolactin Response to Thyrotropin-Releasing Hormone in Children with Gynecomastia, Premature Thelarche and Idiopathic Precocious Puberty.* Tohoku J. exp. Med., 1984, **142** (3), 283-288 — Plasma prolactin (PRL) response to synthetic thyrotropin-releasing hormone (TRH) was studied in six patients with pubertal gynecomastia, five patients with premature thelarche and nine female patients with idiopathic precocious puberty. The basal concentration of plasma PRL was higher ($p < 0.01$) in pubertal gynecomastia as compared to control, while baseline plasma PRL levels in premature thelarche and idiopathic precocious puberty were similar to those in controls. Plasma PRL level after TRH in patients with pubertal gynecomastia was higher ($p < 0.01$) than that in control, while plasma PRL responses to TRH in idiopathic precocious puberty and premature thelarche were comparable to those controls. The TRH-induced PRL release was more enhanced during treatment with cyproterone acetate (CA) than before CA therapy in four of five patients with idiopathic precocious puberty. These data suggest that the enhanced release of PRL may, at least in part, contribute to breast enlargement in pubertal gynecomastia and that seen in idiopathic precocious puberty and premature thelarche may not depend on the PRL secretion. The prolonged administration of CA enhances the PRL responsiveness to TRH. ——— TRH; prolactin; gynecomastia; premature thelarche; idiopathic precocious puberty

The prolactin (PRL) response to synthetic thyrotropin releasing hormone (TRH) has been extensively studied in adults. There is, however, relatively little information on the PRL response to TRH in children (Foley et al. 1972; Kaplan et al. 1972; Okada et al. 1978; Suter et al. 1978; Roitman et al. 1980; Abe et al. 1982, 1983). Since it has been known that PRL plays some role for breast development (Frantz 1981) and that boys who subsequently develop gyneco-

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mastia show an increased PRL level (Lee 1975), we thought it of interest to investigate the PRL response to TRH in clinical disorders associated with breast enlargement. The present study presents data concerning the PRL response to TRH in children with pubertal gynecomastia, premature thelarche and idiopathic precocious puberty.

PATIENTS AND METHODS

Twenty children were referred to the hospital for evaluation of breast enlargement and included in this study. The subjects were divided into three groups on the basis of clinical signs, evaluation of pituitary functions and comprehensive investigation of the central nervous system including brain CT scan.

Group I: six pubertal boys (13–15 years of age) with moderate pubertal gynecomastia. Group II: five prepubertal girls (1–5 years of age) with premature thelarche. Group III: nine girls (2–8 years of age) with idiopathic precocious puberty.

All tests with TRH were performed in the morning after an overnight fast, as previously described (Abe et al. 1979). Synthetic TRH was administered as an intravenous bolus of $5 \mu\text{g}/\text{kg}$ and blood samples were obtained at 0, 15, 30, 60, 90 and 120 min for determination of plasma PRL concentrations. Plasma PRL was measured using a commercially available

Fig. 1. Plasma PRL responses to TRH in 6 patients with pubertal gynecomastia (●—●) and 31 normal boys aged 6–15 years (○---○). Values are mean $\pm$ S.E.M. * $p < 0.01$.

Fig. 2. Plasma PRL responses to TRH in 5 patients with premature thelarche (●—●), 9 female patients with untreated idiopathic precocious puberty (○---○) and 16 normal girls aged 6–10 years (○...○). Values are mean $\pm$ S.E.M.

Fig. 3. Plasma PRL response to TRH in five girls with idiopathic precocious puberty before and during treatment with cyproterone acetate (CA). Left panel and right panel indicate data before and during treatment with CA, respectively.

radioimmunoassay kit (Daiichi Isotope Lab, Tokyo) and human prolactin (hPRL, Lewis No. 3) was used as a reference standard. Statistical analyses were performed using Student's *t* test.

RESULTS

The mean basal PRL concentration was slightly but significantly higher ($p < 0.01$) in boys with pubertal gynecomastia than in thirty-one normal boys aged 6–15 years, while mean basal levels of plasma PRL in girls with premature thelarche and idiopathic precocious puberty were similar to those in sixteen normal girls aged 6–10 years (Figs. 1 and 2). The intravenous administration of TRH elicited significant elevations in plasma PRL in all groups.

The peak level of plasma PRL at 15 min after TRH stimulation was significantly higher ($p < 0.01$) in boys with pubertal gynecomastia than in controls (Fig. 1). However, the peak PRL concentrations in response to TRH in girls with untreated idiopathic precocious puberty and premature thelarche were comparable to those in controls (Fig. 2). Plasma PRL response to TRH in five patients with idiopathic precocious puberty before and one to three years after treatment with cyproterone acetate (CA) at doses of 75–100 mg/m²/day are shown in Fig. 3. The TRH-induced PRL release was more enhanced during treatment with CA than before CA therapy in four of five patients.

DISCUSSION

Previous studies (Turkington 1972; Volpe et al. 1972; Beck 1981) showed that the basal level of plasma PRL in pubertal gynecomastia was comparable to

that in control and Beck (1981) reported the normal PRL response to TRH in boys with marked gynecomastia. On the contrary, the present study demonstrated that the mean basal level of plasma PRL was elevated and its response to TRH was more enhanced in pubertal gynecomastia. In agreement with the present findings, Large and Anderson (1979) and Large et al. (1980) demonstrated elevated 24 hr PRL and estradiol levels in boys with gynecomastia and D'Agata et al. (1977) showed that the administration of sulpiride elicited a greater PRL release in boys with gynecomastia as compared to control. These suggest that patients with gynecomastia have a large pool of acutely releasable PRL in response to provocative stimuli. Since PRL has been known to play some role for breast development (Frantz 1981), the enhanced release of PRL may, at least in part, contribute to breast enlargement observed in gynecomastia. The explanation for the elevated baseline level of plasma PRL and the exaggerated PRL response to TRH may be subtle alterations in dynamics of testosterone and estradiol secretion in gynecomastia, since the relatively high estradiol to testosterone ratio has been observed in pubertal gynecomastia (Large and Anderson 1979) and the increase in estradiol to testosterone ratio is reported to be correlated with peak PRL responsiveness to TRH in primary testicular failure (Spitz et al. 1979).

The present study also showed that there was no significant difference in baseline PRL level or TRH-induced PRL increase between patients with untreated precocious puberty and premature thelarche and normal controls. This suggests that breast enlargement seen in idiopathic precocious puberty and premature thelarche may not depend on the secretion of PRL. On the contrary, Fonzo et al. (1977) described that the mean PRL level and sulpiride stimulated PRL release were significantly higher and more pronounced, respectively, in girls with untreated idiopathic precocious puberty as compared to normal controls. The reason for this discrepancy remains unknown. Moreover, the present study demonstrated that the PRL response to TRH was more enhanced during treatment with CA, although basal concentration of plasma PRL was unchanged. This suggests that CA may exaggerate the PRL responsiveness to TRH and may operate at the hypothalamus or pituitary gland as a stimulatory agent of PRL release. This is in agreement with the finding that PRL secretion in response to TRH was enhanced in patients given CA, but not with the finding that the administration of CA resulted in a significant elevation in baseline level of plasma PRL (Fonzo et al. 1977; Stahnke et al. 1980). This discrepancy may be explained by differences in doses of CA administered and the duration of treatment with CA between their patients and ours.

In summary, the present study demonstrates that the baseline level of plasma PRL and its response to TRH are elevated in pubertal gynecomastia, but these are within normal ranges in untreated idiopathic precocious puberty and premature thelarche. The long-term administration of CA enhanced the PRL responsiveness to TRH in idiopathic precocious puberty.

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