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Amenorrhea-galactorrhea associated with hypothalamic hypothyroidism

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AMENORRHEA-GALACTORRHEA caused by primary hypothyroidism is a well-recognized entity and has been reviewed by Boroditsky and Faiman.¹ Since thyrotropin-releasing hormone (TRH) is also a prolactin-stimulating hormone, one postulate to explain this association is that primary hypothyroidism leads to an

increase in TRH. However, another possibility is that the hypothyroid state causes not only the thyrotroph cell but also the lactotroph cell to become more sensitive to TRH, which results in an increase in prolactin with TRH remaining the same.

The case presented here provides evidence in support of the second hypothesis.

The patient presented at age 27 with a history of 3 years of amenorrhea-galactorrhea since oral contraceptives were discontinued. She had first developed galactorrhea at age 22, 1 year after oral contraceptives were started; she continued to use oral contraceptives for 2 more years. She had not had a spontaneous menstrual period for the 3-year period since the oral contraceptives were stopped to the time that we first saw her. The patient had been receiving no other medication.

She presented at age 25 at another gynecologic endocrine center where no abnormalities on physical examination were found. Laboratory data revealed a low serum gonadotropin level with a follicle-stimulating hormone level (FSH) of 2 MIU/ml and a luteinizing hormone (LH) level of 1 MIU/ml. The serum prolactin level was 150 (normal up to 25) ng/ml. The serum thyroxine level was 5.4 (normal 4.9 to 10.0) μ g/dl. The percentage thyroxine saturation of the total thyroxine binding capacity was 20% (normal 23% to 44%) with an estimated free thyroxine index of 1.08 (normal 1.2 to 2.8) ng/dl. The thyroid-stimulating hormone (TSH) level was 2.2 (normal under 12) μ IU/ml. Despite the slightly low free thyroxine index the patient was judged euthyroid based on the normal TSH value. Treatment with bromocriptine was attempted but stopped because of side effects. A skull x-ray film with tomograms of the sella turcica was normal.

Prior to the patient's initial visit in our office, the spontaneous galactorrhea had ceased, although fluid was still expressible, and this was associated with a drop in the prolactin level from 150 to 77 ng/ml without any therapy. Vaginal hormonal cytologic testing revealed a slight estrogen deficiency, and she failed to have withdrawal bleeding with medroxyprogesterone acetate (Provera), 10 mg for 8 days. A repeat serum prolactin level was 77 ng/ml.

On repeat questioning the patient appeared clinically to be possibly hypothyroid with symptoms of facial puffiness, weight gain, dry skin, decrease in energy, the feeling that "things have slowed down," finding thinking more difficult, and feeling depressed; clinical findings included a heart rate of 68 bpm and a slightly slow bilateral relaxation of the Achilles reflexes. However, the thyroxine level was 6.4 (4.5 to 13) ng/100 ml and the triiodothyronine uptake was 24 (normal 25 to 35) with a free thyroxine index of 1.53 (normal 1.2 to 4.6). The TSH value was normal at 2.3 μ IU/ml. Twenty minutes following 500 μ g of TRH intravenously, the TSH rose from a baseline of 2.9 to 22.9 μ IU/ml. An 8 AM cortisol level was 15.5 μ g/100 ml.

Even though the thyroid studies were in the low normal range with a normal TSH level, because the patient clinically appeared hypothyroid, she was placed on a regimen of 0.15 mg of levothyroxine. Two months later the prolactin level was 33 ng/ml. The fluid of galactorrhea was no longer expressible. At this time she did have withdrawal bleeding following medroxyprogesterone acetate. The patient noted a distinct improvement in the way she felt with improved energy, a decrease in puffiness, normal skin, and an elevation in mood,

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along with a 10-pound weight loss. The heart rate increased to 84 bpm and the Achilles reflexes were normal.

The patient left the Philadelphia area and when the thyroxine prescription was used up she did not get it refilled. She returned to our office 5 months later with a complete return of all previous symptomatology including expressible fluid of galactorrhea. The serum prolactin level had risen again to 68 ng/ml and the serum thyroxine level was 5.8 ng/100 ml. After reinstatement of 0.15 mg of levothyroxine once again the hypothyroid symptoms disappeared as did the galactorrhea, and the serum prolactin level dropped to 29 ng/ml.

Although primary hypothyroidism and amenorrhea-galactorrhea have a well-accepted relationship, secondary hypothyroidism and amenorrhea-galactorrhea are extremely rare. We found one case report in which the patient also had Cushing's syndrome; the abnormality was felt to be a primary hypothalamic disorder.² The elevated prolactin level in that case was attributed to either the effects of glucocorticoid excess or a hypothalamic defect involving an excess of corticotropin-releasing hormone and a deficiency of TRH, LH, FSH, and the prolactin-inhibitory factor (PIF).

In the case we reported, the patient had idiopathic amenorrhea-galactorrhea which may have been made worse by the oral contraceptives. This condition was apparently exacerbated by hypothyroidism since the addition of thyroid hormone dropped the prolactin levels in half to just slightly above normal, stopped the galactorrhea, and allowed enough intrinsic ovarian estrogen production to allow withdrawal bleeding with progestogen therapy.

Since TRH caused a very significant prompt rise in TSH, most likely the defect was in the hypothalamus rather than the pituitary. Thus, this case favors the explanation that the hypothyroid state caused the lactotroph cell to become more sensitive to the stimulatory effects of TRH. Obviously, primary hypothyroidism and galactorrhea would be a more common association because statistically the primary disease is far more common and, second, if the hypothalamic defect is sufficiently great, there may not be sufficient TRH to stimulate the more sensitive lactotroph cell. In view of the low normal thyroid levels in this case, the hypothalamic defect must have been mild. These findings, however, do not negate the possible additional contribution of elevated TRH levels to hyperprolactinemia in cases of primary hypothyroidism associated with amenorrhea-galactorrhea.

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