Galactorrhea in males with tumors in the region of the pituitary gland

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The pathophysiology of galactorrhea in males with pituitary tumors is discussed, two cases are presented, and previously-reported cases are reviewed. Hypersecretion of prolactin is probably the basis for the galactorrhea. Prolactin may be secreted by the tumor itself, or the remaining normal pituitary tissue may oversecrete if the hypothalamus or the pituitary stalk is compressed.

KEY WORDS: galactorrhea • males • pituitary • tumor • prolactin • hypothalamus

Galactorrhea in women with tumors in the region of the pituitary gland has been reported frequently in the past. However, its occurrence in males with pituitary tumors is rare.

Roth, in 1918, reported a 28-year-old acromegalic man with decreased visual acuity and bitemporal hemianopsia who had galactorrhea. He had much adipose tissue about the breasts and had underdeveloped testes. In 1928 Haenel reported a 43-year-old man with small testes, severe headaches, and galactorrhea but no visual disturbances; at autopsy he had an “angiosarcoma” of the pituitary. In 1940 Staemmler reported a 26-year-old acromegalic man with galactorrhea. McCullagh, et al., in 1956, reported a 26-year-old man with pituitary tumor, gynecomastia, and lactation. Following irradiation the lactation persisted.

We have treated two young men with galactorrhea as the presenting sign of a pituitary tumor. Since one patient admitted having had galactorrhea only upon specific questioning, we wondered if this condition might be more common than is generally thought, and therefore undertook a review of all male patients with pituitary tumors treated in this institution in the past 10 years. This review failed to reveal a single case, however. The purpose of this paper is to discuss current concepts of the mechanism involved in galactorrhea with pituitary tumors and to describe our cases.

Case Reports

Case 1

This 18-year-old South American University student had a 1½-year history of galactorrhea and a 1-month history of pain in the left occiput. There were no visual disturbances and no abnormal bone growth. There were no sexual difficulties and he had undergone a normal puberty. He had been taking no medications.

Examination. The patient was normal-appearing with normal secondary sexual characteristics. Milky fluid could easily be expressed from both nipples. There was no gynecomastia. The neurological examination, including visual fields, was completely normal.

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FIG. 1. Case 1. Pneumoencephalogram showing double floor of sella turcica and no suprasellar extension of pituitary tumor.

Laboratory and Special Studies. Complete blood count, urinalysis, glucose tolerance test, bleeding time, clotting time, serum calcium, phosphorus, protein-bound iodine, thyroxine by column, and T-3 resin uptake were all normal ACTH stimulation was normal, with plasma corticoids at 10.5 μg% before ACTH and 34.3 μg% following, and both 24-hour urinary 17-ketosteroids and 17-ketogenic steroids were likewise normal at 10.9 mg per day and 12.2 mg per day respectively. Total urinary gonadotropin by the mouse uterine weight method was low normal at 5 mouse units. Human growth hormone determination done in conjunction with a glucose tolerance test revealed borderline low values, initially 1.1 (μg/ml), at 30 min 1.2 μg/ml, at 60 min less than 0.2 μg/ml, at 120 min 0.2 μg/ml, and at 180 min less than 0.2 μg/ml. The prothrombin time was 15 with a control of 13. The sedimentation rate was 39. Spinal tap revealed four white blood cells and 1372 red cells; the supernatant fluid was clear and colorless. Skull films revealed a double-floored sella turcica. Pneumoencephalogram showed an intrasellar mass without suprasellar extension. A right carotid arteriogram suggested a suprasellar mass.

Hospital Course. The patient was started on a course of radiotherapy. After several days he began to complain of headache and a stiff neck and a lumbar puncture revealed bloody spinal fluid. He was kept at bedrest and over the next week improved considerably. Left carotid and bilateral brachial arteriograms were done, as well as x-rays of the lumbar spine, to search for a cause of his subarachnoid hemorrhage, but these were normal. The remainder of his hospital course was uneventful. At the time of discharge he felt well; he had received 4500 R and the galactorrhea persisted. Several weeks following discharge the galactorrhea ceased, and he has remained asymptomatic for the past 2 years.

Case 2

This 32-year-old man had a 1-year history of left-sided headaches and blurring of vision in the left eye. He was treated for glaucoma by an ophthalmologist with no improvement in symptoms, and he then consulted an ophthalmologist at Columbia-Presbyterian Medical Center who obtained skull films which revealed an enlarged sella turcica. Upon close questioning he revealed that he had had a discharge from the left nipple for 1 year prior to the onset of his other symptoms but had mentioned it to no one other than his wife. He denied sexual difficulties, decreased libido, impotence, excess fatigue,

FIG. 2. Case 2. Pneumoencephalogram showing a considerably enlarged and eroded sella turcica with some suprasellar extension of pituitary tumor.
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change in appearance, or change in the shape of his hands.

Examination. The patient was a well-developed, normal-appearing man with minimal gynecomastia bilaterally. Compression of the left breast produced a watery-milky secretion. The genitalia were normal. Neurological examination was normal. Vision was 20/15 bilaterally. Visual fields showed a slight left temporal field defect.

Laboratory and Special Studies. Complete blood count, urinalysis, fasting blood sugar, glucose tolerance test, cholesterol, blood urea nitrogen, serum VDRL, serum calcium, and phosphorus were all normal. The 24-hour urinary 17-ketosteroids and 17-ketogenic steroids were normal at 18.2 mg per day and 12.8 mg per day respectively. Radioactive iodine uptake was low, at 11%, as was serum protein-bound iodine at 3.7 g%. Growth hormone levels, done in conjunction with a glucose tolerance test, were low, initially 0.3 μg/ml, at 30 min less than 0.3 μg/ml, at 60 min 0.4 μg/ml, at 120 min 0.3 μg/ml, and at 180 min less than 0.3 μg/ml. The ACTH stimulation was borderline low, with plasma corticoids at 13.4 μg% prior to ACTH and 32.6 following. Total urinary gonadotropin by the mouse uterine weight method was not detectable. The prolactin level, measured by an in vitro assay utilizing breast tissue fragments from pregnant mice, as reported by Frantz and Kleinberg,19 was markedly elevated at 14 milliunits per milliliter.

The electrocardiogram was normal. Skull films showed a considerably enlarged sella turcica. Pneumoencephalogram revealed an intrasellar mass with minimal suprasellar extension.

Hospital Course. The patient was started on a course of radiotherapy. Over the next 2 weeks the visual field defect diminished slightly. He suffered no untoward effects of radiation. The galactorrhea was still present at discharge but ceased during radiotherapy and has not recurred. He continues to do very well after 2 years of follow-up.

Discussion

Although galactorrhea from all causes is relatively rare, the list of conditions known to be associated with this disorder is long. Intracranial tumors which have been associated are chromophobe, eosinophilic, and basophilic adenomas of the pituitary, craniopharyngioma, pinealoma, and "angiosarcoma." Tumors of the adrenal, testes, ovaries, uterus, and adnexa have also been reported. In addition, certain states of hormonal imbalance such as hyper and hypothyroidism, hypopituitarism, and hypogonadism can be associated with galactorrhea. It can follow pituitary stalk section and also hysterectomy. Various neurological diseases can lead to galactorrhea, including pseudotumor cerebri, encephalitis, hypothalamic infarction, tabes dorsalis, syringomyelia, and pseudocyesis. Finally, diseases of the breast or of the skin of the chest wall are reportedly associated.

Several syndromes of abnormal lactation of obscure etiology have been described. Chiari, et al.,4 in 1855, and Frommel,11 in 1882, described a syndrome of persistent postpartum lactation in the absence of suckling, associated with amenorrhea, uterine and ovarian atrophy, psychosis and other psychiatric disturbances, and malnutrition. These patients generally have a low or absent urinary gonadotropin. The etiology is unclear but may be related to the enlargement of the pituitary which is known to occur during pregnancy,9 and some of these cases are probably associated with pituitary tumors.

Forbes, et al.,8 described a syndrome of galactorrhea, amenorrhea, and low urinary FSH not associated with a recent pregnancy. Fifty per cent of these women had evidence of a pituitary tumor. Argonz and Del Castillo1 described the same syndrome but their patients were all nulliparous and none had evidence of a pituitary tumor. Hardy15 suggested that the patients who manifest the above syndromes without an enlarged sella turcica may harbor micro-tumors of the pituitary, and he believes that they should be explored microsurgically.

The mechanism of galactorrhea in association with pituitary tumors is not clear, but it is likely that a hypersecretion of prolactin is of prime importance. Prolactin, also known as lactogenic hormone or mammotrophin, is a protein hormone which has been isolated in relatively pure form from the pituitary glands of several species of animals. The complete sequence of 198 amino acids in

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sheep prolactin has been reported recently. The status of prolactin in human beings is less clear, since human growth hormone itself is strongly lactogenic, and definitive characterization of a separate human prolactin has not yet been achieved. Nevertheless, considerable clinical and experimental evidence suggests that prolactin does exist as a separate hormone in man and that its secretion is governed by mechanisms different from those that control growth hormone.

Prolactin has generally been difficult to quantitate, the standard method being a bioassay based on the response of the pigeon crop-sac. A more sensitive assay utilizing breast tissue fragments from pregnant mice has been developed recently. By this method high prolactin levels, together with low growth hormone, have been demonstrated in the blood of normal nursing mothers, as well as in patients with galactorrhea due to other causes. Animal studies indicate that prolactin contributes to the initiation and maintenance of milk production in the breast which has been appropriately prepared by a combination of estrogen and progesterone.

There are various factors that control prolactin secretion. Low levels of estrogen appear to enhance prolactin secretion by a direct effect on the pars distalis of the pituitary, while high levels inhibit it, probably by an effect upon the hypothalamus. Progesterone inhibits the ability of estrogen to stimulate prolactin secretion. There is frequently a reciprocal relationship between gonadotropin and prolactin levels.

In addition to relationships with levels of circulating hormones prolactin is also influenced by the hypothalamus, which appears to exercise an inhibiting effect. Prolactin secretion by the pituitary is enhanced by lesions in the arcuate and ventromedial nuclei of the hypothalamus, by hypophyseal stalk section, and after pituitary transplantation. Prolactin production in tissue cultures can be inhibited by hypothalamic homogenates or extracts, strongly suggesting the existence of a specific prolactin inhibitory factor (PIF). During normal lactation the sucking stimulus initiates an impulse which traverses the spinal cord and brain stem and causes the hypothalamus to release its inhibiting effect upon prolactin secretion. This mechanism, in combination with the stimulating effects of estrogen now, in the postpartum period, unrestrained by progesterone, leads to normal lactation.

There are several possible explanations for the occurrence of galactorrhea in patients with pituitary tumors. One is that the tumor itself secretes prolactin. A patient with the Forbes-Albright syndrome has been found to have an eosinophilic pituitary adenoma which was prolactin-rich. The eosinophilic granules were different from growth hormone granules in size, shape, and staining characteristics, which suggests that this was a tumor of prolactin-secreting pituitary cells. The authors raise doubts about earlier histological studies of chromophobe adenomas associated with amenorrhea and galactorrhea, suggesting that preservation of the granules by a special fixative may reveal an eosinophilic adenoma. They also mention that most pituitary tumors that appeared degranulated by light microscopy have been found by electron microscopy to contain granules and that chromophobe cells of the pituitary have been shown to contain granules.

Another mechanism by which a pituitary tumor could cause galactorrhea is by hypothalamic compression, destroying its ability to inhibit pituitary prolactin production and release. The hypothalamic lesions in rabbits produced by Haun and Sawyer with resultant galactorrhea would support this concept. Also, a tumor that compresses the pituitary stalk could release the prolactin-secreting cells from the inhibiting effect of the hypothalamus, causing a hypersecretion, with subsequent lactation. This is thought to be the mechanism of the lactation that follows surgical section of the pituitary stalk.

Another hypothesis involves hormonal overlap in pituitary feedback. It is known that galactorrhea occurs in cases of primarily decreased thyroid and ovarian hormone production. It also occurs in Sheehan's syndrome and in partial hypopituitarism. As target organ production decreases, whether primarily, or secondary to decreased tropic hormone, the remainder of the tropic hormones, including prolactin, may oversecrete, in an overlapping response. A tumor, by causing partial hypopituitarism, could in this way cause galactorrhea.

In order for galactorrhea to develop, a
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prolactin-responsive breast is necessary, which explains its extreme rarity in males. To produce galactorrhea in the male, a state of hormonal balance must be produced which not only primes the breast but stimulates it as well to produce milk. This series of events has yet to be fully elucidated. It is interesting in this regard to note that while the patient reported by McCullagh, et al., had marked gynecomastia, our cases did not.

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