Clinical Endocrinology

Galactorrhoea

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Pathological galactorrhoea is the secretion of milk from the breasts which is inappropriate to the physiological status of the patient—in other words, the patient is not, or has not recently been, pregnant. Certainly a little milky secretion can often be expressed from the breasts of multipara, but any more than this (especially if associated with amenorrhoea) or any lactation in males is a significant abnormality. Normal babies often secrete small amounts of milk after delivery, probably as a result of temporary secretion of prolactin by the baby's own pituitary,[1] though initially exposure of the fetus in utero to the placental lactogenic hormone may be involved.

Until the recent introduction of sensitive and specific bioassays for measuring plasma concentrations of the pituitary hormone prolactin, the cause of inappropriate lactation in the many conditions in which it has been described has not been clear. Nevertheless, it now appears that plasma prolactin levels are raised in patients with galactorrhoea and that the hyperprolactinaemia is causally related to the inappropriate lactation. Now much more sensitive radioimmunoassays are being developed which can measure normal plasma levels of the hormone and these should allow study of the physiological mechanisms which control its secretion.

Associated Clinical Conditions

The common clinical associations of galactorrhoea are shown in Table I. Of the pathological causes, drug-induced galactorrhoea is the most common. In women, the pituitary group of causes has in the past been divided into three main subgroups depending on the mode of onset of the disease and the radiological appearances of the pituitary fossa; in each group amenorrhoea usually accompanies galactorrhoea.

In the so-called Chiari-Frömmel syndrome galactorrhoea and amenorrhoea develop postpartum, whereas in the Argonz-del Castillo syndrome they are unrelated to pregnancy. In both syndromes the pituitary fossa is normal. Patients with abnormal pituitary fossae suggesting the presence of a pituitary tumour, and lactation developing either postpartum or spontaneously, have been assigned to yet another eponymous group, the Forbes-Albright syndrome.

This classification is of little value in understanding the pathophysiological mechanisms involved and cases have been described which have evolved through all three syndromes,[2] and some eventually have developed Cushing's disease[3] or acromegaly. It is now quite clear that all three of these classical syndromes in women, as well as galactorrhoea in men, are associated with the secretion of excessive prolactin.

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Prolactin Physiology

Though possibly many different hormones are involved in the maintenance of normal lactation (for example, oestrogens, progesterone, corticosteroids, and thyroxine)[4] probably prolactin is the most important hormone associated with pathological lactation.[5–7] It is only recently that prolactin has been accepted as a definitely distinct anterior pituitary hormone in man, separate from growth hormone.[5 6 8]

The release of prolactin is primarily controlled by a hypothalamic inhibitory factor, though there is also evidence for a prolactin releasing factor. Thyrotrophin releasing hormone appears to cause the release of pituitary prolactin,[9] though it is not clear whether the former is identical with the physiologically important prolactin releasing factor. However, under normal circumstances prolactin secretion from the pituitary is maintained under tonic inhibition by the hypothalamic inhibitory factor and it is the removal of this inhibition which results in hyperprolactinaemia and galactorrhoea in lesions of the hypothalamus or pituitary.

The physiological factors which modify the inhibitory factor and prolactin secretion are poorly understood. Prolactin is released by sucking and stress and possibly by insulin-induced hypoglycaemia. It may be suppressed by hyperglycaemia. The release of prolactin and the gonadotrophins seems to be interrelated, as indicated by the frequent association of amenorrhoea with galactorrhoea, and the presence of low plasma gonadotrophin levels which fail to rise during administration of clomiphene (normally clomiphene acts on the hypothalamus to cause gonadotrophin release.) Successful suppression of the oversecretion of prolactin is usually followed by restoration of regular menstruation and normal gonadotrophin levels, which rise after the administration of clomiphene.

Rarely galactorrhoea occurs in men and this is usually associated with impotence, suppressed plasma gonadotrophin levels, and an absent response to clomiphene.

Pathophysiology of Prolactin Release

Many centrally acting drugs, and particularly phenothiazines, inhibit the release of prolactin inhibitory factor from the hypothalamus and thus cause the release of prolactin. Oestrogens also increase the secretion of prolactin, though the precise mechanism is not clear.

In patients with the hypothalamic type of hypopituitarism a lesion in the hypothalamus or affecting the portal-capillary system of the pituitary stalk prevents the normal tonic inhibition of prolactin secretion by prolactin inhibitory factor.

There is additional evidence that patients with tumours of the pituitary itself in association with galactorrhoea may have autonomous production and release of prolactin. Possibly the plasma prolactin response to a rise in blood glucose may indicate whether a pituitary lesion remains under hypothalamic control, since it has been reported that patients without radiological evidence of pituitary tumour show definite suppression of their high prolactin levels during a glucose tolerance test, while patients with pituitary tumours show no suppression.[5]

TABLE I—*Causes of Galactorrhoea*

- Physiological
  - During pregnancy*
  - Postpartum*
  - Neonatally*
- Pathological
  - Pituitary tumours
    - Apparently otherwise non-functioning adenomas*
    - Cushing's disease
    - Acromegaly*
  - Partial hypopituitarism—any cause
    - Idiopathic
    - Posttraumatic
    - After pituitary stalk section*
    - Postpartum necrosis
  - Hypothalamic disorders
    - Lesions affecting median eminence and pituitary stalk*
    - Postencephalitic parkinsonism
    - Encephalitis, basal meningitis
    - Pineal tumour (psammosatcoma)
  - Primary hypothyroidism with either amenorrhoea* or precocious puberty
  - Hyperthyroidism
  - Oestrogen-secreting tumours, choriocarcinoma of testis
  - Local factors
    - Thoracic surgery
    - Injuries to chest wall
    - Herpes zoster of chest
  - "Ectopic" production of prolactin by non-endocrine tumours
- Drug-induced
  - Phenothiazines*
  - Oral contraceptives,* oestrogens*
  - Rauwolfia alkaloids*
  - Imipramine*
  - Haloperidol*
  - Methyl dopa*

* Hyperprolactinaemia demonstrated

Galactorrhoea associated with acromegaly may be due to the intrinsic lactogenic activity of growth hormone, but possibly there is a concomitant release of prolactin, since the prolactin levels are often much higher than can be accounted for by growth hormone alone. "Ectopic" production of prolactin by non-endocrine neoplasms in association with galactorrhoea has also been described.[10]

Patients with gynaecomastia without galactorrhoea have undetectable prolactin levels as measured by bioassay and there is no evidence that this hormone is concerned in its development.[5] "Simple" gynaecomastia often appears to be associated with oestrogen concentrations which are above effective androgen activity, as in patients with testicular tumours that are secreting oestrogens. Alternatively it may be related to altered gonadotrophin secretion, as at puberty or in patients given chorionic gonadotrophin; under these circumstances, however, the effect may also be mediated by increased gonadal oestrogen secretion stimulated by the gonadotrophins. In patients being treated with testosterone gynaecomastia without galactorrhoea is not uncommon and seems to be related to conversion of testosterone to oestrogenic metabolites in the peripheral tissues.

It is becoming increasingly obvious that the amenorrhoea which may follow oral contraceptive therapy is sometimes accompanied by modest galactorrhoea[11 12] and may also be associated with hyperprolactinaemia. If the amenorrhoea spontaneously disappears the galactorrhoea also ceases.

Prolactin Assays

In the past, attempts have been made to measure plasma prolactin levels in patients with galactorrhoea using the insensitive pigeon crop assay.

More recently bioassay methods using the lactogenic response of cultured lobular-alveolar rabbit or mouse mammary tissue has been introduced.[8 13] These assays are more sensitive and specific since only prolactin, growth hormone, and human placental lactogen induce a response, but have the disadvantage that they use a histological end point and are thus only semi-quantitative. In addition they are very time-consuming to perform. Recently induction of the specific milk protein, casein, into the breast cultures has also been used as a measure of prolactin activity. Since human growth hormone produces a lactogenic response in all these bioassays, growth hormone levels should be measured by radioimmunoassay on all samples sent for prolactin bioassay, using antisera previously shown not to cross-react with prolactin. Only when the plasma growth hormone concentrations have been shown to be far lower than could account for the lactogenic activity seen in the bioassay system can such activity be accepted as being due to prolactin itself. Such a system has been used to show the aetiological relationship of prolactin to galactorrhoea in patients.[5 7] Specific radioimmunoassays for prolactin with greater sensitivity are being currently developed and should amplify the earlier findings.[1]

Investigation

A protocol for the investigation of patients with galactorrhoea is shown in Table II

TABLE II—*Investigation of Patients with Inappropriate Lactation*

The following steps are usually required:

(1) Full drug history and possibly analysis of urine and blood for relevant drugs and their metabolites

(2) Evaluation of anterior pituitary function:
- GH, ACTH—insulin tolerance test
- Thyroid—see below (3)
- Gonadotrophins—LH, FSH, and sex hormone assays under basal conditions and during clomiphene administration

(3) Thyroid function:
- Basal protein bound iodine, resin T-3 test, radioiodine uptake (before and after TSH administration if hypothyroid)
- Serum TSH assays before and after TRH administration when possible.
- Antithyroid antibody studies.

(4) Radiology:
- Skull *x*-ray films, with pituitary tomography if necessary
- Air encephalogram if indicated by change in visual fields or presence of diabetes insipidus

Treatment

This should be directed towards the underlying cause, if possible. In patients with primary hypothyroidism, amenorrhoea, and galactorrhoea the high prolactin levels fall, menstruation returns, and the galactorrhoea disappears on thyroxine therapy alone.[6] Phenothiazine and other drug-induced galactorrhoea is usually transient and stops with cessation of the drug. In contrast, in patients with amenorrhoea and galactorrhoea induced by the contraceptive pill galactorrhoea may be prolonged. In these patients the amenorrhoea may respond to clomiphene or gonadotrophin therapy inducing ovulation and reducing the galactorrhoea, but the effects are often only temporary.

Until recently the most difficult group of patients to treat have been those with organic pituitary or hypothalamic disease. Some of these require definitive treatment of a pituitary tumour by surgery if there are defects of the visual fields. Unfortunately this may worsen the galactorrhoea, since any remaining pituitary cells are likely to be completely separated from the inhibitory influence of the hypothalamus. Pituitary irradiation rarely improves galactorrhoea or amenorrhoea. In these patients, and the many others without evidence of a pituitary tumour, treatment with oestrogens or progesterone has often been advocated in the past but is rarely successful. Though L-dopa has been shown to suppress plasma prolactin levels in these patients, unfortunately the effect is transient and so far appreciable relief of the galactorrhoea has not been achieved with this drug.[14] By contrast, the administration of a newly introduced ergot alkaloid, 2-Br-alpha-ergocryptine (CB 154) appears to relieve the galactorrhoea, often within a few days, and is associated with return of menses. The early clinical evaluation has been encouraging[15] and subsequent, as yet unpublished, observations show that it works in both men and women, results in appreciable reduction in plasma prolactin concentrations with return of normal gonadotrophin secretion, menstruation in women, and potency in men. The clomiphene-induced rise in gonadotrophins and gonadal steroid hormone secretion return to normal and, in men, the breast glandular tissue and fat shrink and body fat is redistributed in a normal pattern. It also seems to be effective in suppressing postpartum lactation, and galactorrhoea occurring as a result of taking the pill. This compound, unlike some other ergot alkaloids, is devoid of α-adrenergic blocking activity and appears to act directly on the pituitary gland itself to suppress prolactin release. The precise mechanism is not clear, but the reduction in prolactin secretion appears to allow normal gonadotrophin release. This drug is unlikely to be of benefit in simple gynaecomastia, and the best treatment in this condition is plastic surgery if the condition is severe enough to cause embarrassment.

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Scientific Basis of Clinical Practice

Antidiuretic and Growth Hormones

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Antidiuretic hormone (ADH) and oxytocin are thought to be secreted by the neurones in the supraoptic nucleus and the paraventricular nuclei of the hypothalamus, ADH mainly or entirely in the former and oxytocin in the latter. The neurones, and their axons which form the hypothalamico-hypophyseal tract, contain neurosecretory granules consisting of neurohypophyseal hormone bound to the protein, neurophysin. The tract terminates in the posterior lobe of the pituitary, where the nerve endings are rich in neurosecretory granules.[1] The pituitary cells (pituicytes) were formerly thought to be secretory but are now known to be a neuroglial type of cell.

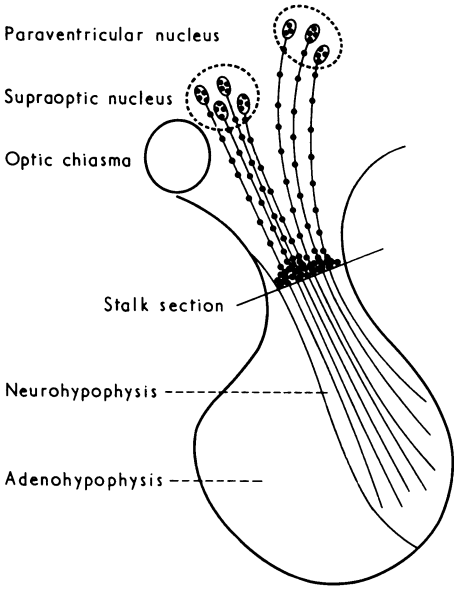

FIG. 1—Diagram showing accumulation of neurosecretory material at the proximal cut end of the hypothalamico-hypophyseal tract after section of the pituitary stalk.[2]

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In vivo the neurosecretory granules migrate down the hypothalamico-hypophyseal tract at a speed of about 3 mm per day. If the tract is cut granules accumulate above the cut and disappear below (Fig. 1[2]). Vascular reorganization can occur above the cut with subsequent release of the hormones and this is why diabetes insipidus is usually only a temporary sequel of hypophysectomy unless the greater part of the pituitary stalk has been removed together with the gland.

Stimulation of the supraoptic and paraventricular nuclei provokes action potentials in the hypothalamico-hypophyseal tract, and the resultant depolarization of the nerve endings in the neurohypophysis causes release of neurosecretory granules. Release of the neurohypophyseal hormones depends on the presence of calcium, as does the release of insulin, thyroid-stimulating hormone, luteinizing hormone, and adrenaline.

After release, the neurohypophyseal hormones become dissociated from neurophysin, which also enters the circulation.

Actions of ADH

In a person without renal disease the 15% or so of the glomerular filtrate which enters the distal convoluted tubules of the nephrons is hypotonic because sodium has been reabsorbed from the ascending limb of the loop of Henle without the reabsorption of an equivalent amount of water. In the absence of antidiuretic hormone the distal tubules and the collecting ducts are relatively impermeable to water, and hypotonic urine with an osmolarity of approximately 100 mOsm/litre (specific gravity 1·003) is formed. This occurs in severe diabetes insipidus and 20 litres or more are excreted a day.

ADH increases the permeability of the distal convoluted tubules and collecting ducts. When the hormone is present the increasing concentration of solutes in the interstitial fluid towards the tips of the renal papillae causes reabsorption of water by osmosis. If there is sufficient ADH the urine becomes isotonic with the interstitial fluid in the papillae and the osmolarity reaches about 1200 mOsm/litre (specific gravity 1·030), which is the level found in a normal subject deprived of fluid.

The effect of ADH on the kidney may be detected within two to four minutes of intravenous injection. The hormone is an octapeptide containing a cystine residue. It has been suggested that ADH binds to receptor cells by the formation of covalent linkages between the disulphide bridges of the cystine residues