

Nipple discharge and fear of cancer

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This is the first in a series of endocrine enigmas. Your patient has had nipple discharge for about a year and she's worried she may have cancer. What could be the cause of the discharge?

Case scenario

Jane, a 34-year-old woman, comes to see you. She is concerned about her nipple discharge, which she later demonstrates to you (Figure). The discharge has been present for 'about a year'. She wasn't worried about it at first, but there's more of it now, her breasts are lumpy and she's worried she may have cancer.

Jane had menarche at the age of 11, regular periods (mostly with a contraceptive pill), and two pregnancies when she was aged 28 and 32 – with healthy infants whom she breastfed for three and five months respectively.

She is overweight: weight 64 kg, height 158 cm, BMI 25.6 kg/m². (Overweight BMI is 25 to 30 kg/m². As a rough rule, healthy weight [kg] = height [cm] – 100; in Jane's case 158 – 100 = 58 kg). She is otherwise well and has had no major illnesses.

Her medications include the oral contraceptive pill and sertraline (Zoloft), which was started three months after the birth of her second child. She also takes a range of health foods including garlic,

ginkgo and multivitamins.

Your examination confirms the discharge but shows no other significant abnormality.

You arrange to check her prolactin value. It is 84 µg/L (normal range, <20 µg/L).

Questions

- Is a pituitary prolactin tumour likely to be present? If so, why? If not, why not?
- What medications cause hyperprolactinaemia?
- What further biochemical investigations are indicated?
- Is a CT scan appropriate? If so, why? If not, why not?

Feedback

Is a pituitary prolactin tumour likely to be present?

No, a pituitary prolactin tumour is not likely to be present. As a rough guide, prolactin values less than 100 µg/L (i.e. five times the upper limit of normal) are probably not associated with a prolactinoma, and values greater than 200 µg/L are. Jane's prolactin value is 84 µg/L.

The other useful indicator is amenorrhoea. Approximately 20% of women with either galactorrhoea or amenorrhoea have a prolactinoma compared with 50% of those who have both. Jane is taking



Figure. The milky discharge of galactorrhoea.

oral contraceptive pills so her menstrual status is not helpful.

What medications cause hyperprolactinaemia?

Medications that may cause hyperprolactinaemia are listed below in Table 1.¹ Remember that prolactin is under hypothalamic control – with stimulation by thyrotrophin releasing hormone and inhibition by dopamine. Medications interfering with dopamine (e.g. phenothiazines) increase prolactin. Factors such as stress also work through hypothalamic

Table 1. Medications that may cause hyperprolactinaemia¹

Common

Antipsychotics
Clomipramine
Domperidone
Metoclopramide
Selective serotonin reuptake inhibitors

Less common

H₂-receptor antagonists
Methyldopa
Monoamine oxidase inhibitors
Oestrogens
Tricyclic antidepressants
Verapamil

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Table 2. Medical conditions causing hyperprolactinaemia

Common

- Idiopathic causes
- Pregnancy
- Primary hypothyroidism
- Polycystic ovary syndrome

Less common

- Prolactin-secreting pituitary tumours

Rare

- Other large pituitary tumours
- Chronic renal failure
- ‘Big prolactin’*
- Extreme chest wall stimulation (e.g. in burns)

*Aggregates of prolactin that accumulate and cause high assay readings.

influence. Oestrogen makes the prolactin secreting cells more responsive to stimuli (hence its effect in pregnancy), and nipple stimulation also gives positive feedback (hence the influence of suckling).

Jane is taking two medications that can cause hyperprolactinaemia: oestrogens and a selective serotonin reuptake inhibitor (sertraline). In the absence of any other cause (see below), Jane could be observed or she might like to stop both medications and check that the galactorrhoea and hyperprolactinaemia resolve.

If she remained concerned about cancer in spite of your explanation, a breast ultrasound or mammogram might reassure her.

What further biochemical investigations are indicated?

It’s always worth confirming an abnormal biochemical result, although Jane’s pro-

lactin value fits with the clinical picture. Prolactin has a diurnal rhythm and is affected by food intake, so checking her fasting value would be useful to confirm the abnormality and to establish a clear baseline for further monitoring.

The common medical causes of galactorrhoea plus amenorrhoea are listed in Table 2. In this case, pregnancy is unlikely given the time sequence and the regularity of Jane’s periods since puberty, and her fertility makes polycystic ovary syndrome unlikely. Asymptomatic hypothyroidism is always a possibility. A non-prolactin-secreting pituitary tumour is possible, but normal levels of free thyroxine (T4) and thyroid stimulating hormone (TSH) would make this extremely unlikely. Therefore, all that is usually needed is to confirm the abnormality, do a pregnancy test, and measure free T4 and TSH levels.

In a substantial proportion of women with galactorrhoea and a prolactin value of less than 100 µg/L no cause is found. In these cases, observation is quite appropriate. For example, in one series only one of 59 women developed a prolactinoma and many abnormalities spontaneously resolved.

Is a CT scan appropriate?

No, a CT scan is not appropriate. Jane's prolactin value is low and does not suggest a prolactinoma. On the information available (galactorrhoea alone), the probability of a prolactinoma is 20%. She is taking medication known to cause hyperprolactinaemia, therefore the likelihood of a prolactinoma is even less.

At least 5 to 10% of the CT images of the pituitary requested for suspected hyperprolactinaemia or prolactinoma and reported as consistent with a micro-

adenoma are false positives.

Let us assume Jane has a 10% chance of having a small prolactinoma and the CT scan is 80% likely to show it. If 100 women like Jane had a CT scan, 10% of the women would have a prolactinoma and the CT scans would be positive in eight (80%), and 90% of the women would be normal but the CT scans would be 'positive' in nine (10%).

In these circumstances, a positive scan is actually more likely to be associated with normality than pathology (in nine of 17 'positive' scans). You, Jane and her family would be unnecessarily concerned and might well embark on further potentially confusing investigation.

If the clinical and biochemical assessment is consistent with a pituitary tumour, a CT scan can exclude a macroadenoma (which can cause hyperprolactinaemia by damaging the pituitary stalk), but an

MRI scan is needed to accurately define hypothalamic pituitary morphology.

Keypoints

Prolactin values less than five times the upper limit of the reference range are unlikely to be associated with a prolactinoma. In these women, confirming the raised prolactin and checking a pregnancy test and thyroid function (free T4 and TSH) are the only investigations indicated. Medication is the commonest cause of hyperprolactinaemia. The women in whom a medical cause is not found should be observed and their prolactin levels monitored.

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Reference

1. Davies PH. Drug-related hyperprolactinaemia. *Adverse Drug React Toxicol Rev* 1997; 16: 83-94.