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How to Investigate Bilateral Breast Nipple Discharge: An Account of Extra-mammary Causes and their Management

Asif Hussain

IMPORTANCE Nipple discharge is a common presentation with multiple causes including physiological, systemic and breast related causes. Investigations and management depend on the underlying cause. Detailed history & examination is often very helpful and investigations can confirm the clinical suspicion. This review is mainly focused on extra-mammary or systemic causes of breast discharge. Systemic causes are mainly investigated by medical team but many cases will need surgical input to fix the cause such as prolactinoma.

KEYWORDS Nipple Discharge, Mammary Causes, Extra-mammary Causes

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Invited Review

Corresponding Author: Dr Asif Hussain, MBBS (Honors), MRCP (UK), FRACP, MSc (UK) Clinical Director Medical Specialties Epping Family Medical Specialist Centre
drasifhussain@gmail.com
0061-4-23308681
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Nipple discharge is a common complaint in females. It can be expected if it's within two years of delivery or during pregnancy or after abortion or intentional termination of pregnancy in the second trimester, in the absence of any sinister symptoms or signs. When it's abnormal, the cause can be local within the breast or systemic. Local causes in the breast can be benign (duct ectasia, Fibrocystic disease, ductal papilloma, mastitis, etc.) or malignant. Approximately 5-7% of cases of nipple discharge are due to Breast cancer[1], [Table 1].

Nature of the discharge	Etiologies	Unilateral/ Bilateral	Ducts involved.
Milky	Hyperprolactinemia Post-partum, Medications Chiari-Frommel syndrome.	Bilateral	Multiple
Serous/ Serosanguinous	Intraductal papilloma/ Papillomatosis Intraductal carcinoma.	Unilateral	One or two
Blood	Papilloma / papillomatosis Cancer, Trauma, Infection	Unilateral	One or two
Green	Fibrocystic disease	Bilateral	Multiple

Table 1: Nature of the discharge and possible etiologies

Physiological Vs. Pathological Nipple Discharge:

Clues for pathological discharge include non-lactational, persistent, spontaneous, coming from one duct, unilateral, serosanguinous, no cyclical variations, lump in the breast, lymphadenopathy, breast skin, or nipple changes. Chances of being malignant increase when blood-stained, unilateral, with a lump, past or family history of breast cancer, and the patient is 50 years or above. Multiple duct discharges are rarely malignant [2]. Work up for the local causes will include history, examination, mammogram, ultrasound breast, cytological examination, ductography, ductoscopy, biopsy, and resection [Table 2].

Types of discharge	Investigations	Treatment
Physiological	None	Reassurance
Systemic etiology	Prolactin, Growth hormone, FSH, LH, Oestradiol, Testosterone Thyroid functions, renal & Hepatic functions. Pelvic USS for PCOS MRI Pituitary-Hypothalamic area	Treat the cause Dopamine agonists Somatostatin analogues Pituitary surgery / radiotherapy
Local cause within breast	Mammography, USS Breast, Cytology, Ductography, Ductoscopy, Biopsy.	Treat the cause Surgical &/or XRT &/or Chemotherapy depending on the cause.

Abbreviations: FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone), PCOS (poly Cystic Ovarian Syndrome), USS (Ultrasound), XRT (Radiotherapy).
Table 2: Summary of the investigations and management.

Investigations to exclude any local cause:

1. Mammography: It's the first line and may show microcalcifications, change in breast tissue density. It has a 10% false-negative and 1-2% false-positive rate for detection of breast cancer in patients with nipple discharge. Mammography can findings should correspond to the area of the release.[3]
2. Ultrasound is complementary to mammography and may also help to take a biopsy. It can see 0.5 mm-sized

intraductal lesions. It may show hyperechoic (papilloma), calcified irregular, and margins with hypoechoic non-uniform lesions are usually carcinoma. Duct ectasia will show multiple dilated ecstatic subareolar tubules.

3. Cytology of the discharge or the sample obtained by ductoscopy or duct lavage is very useful. However, false-negative results are a drawback.
4. Ductography and dye localization of the ductal lesions. However, it can only be done if the nipple discharge is reproducible and if cannulation is possible. It can detect duct irregularities, filling defects, cut-off signs & helps localization of the lesion, which can assist biopsy/resection, hence increasing the yield of the surgical approach from 67% to 99%. It doesn't differentiate benign from malignant and doesn't specify underlying pathology [4, 5]
5. Duct endoscopy can help visualize the ducts and obtain samples and possible therapeutic options such as resection of the lesions[6].
6. Surgical biopsy by terminal duct excision is performed for pathological nipple discharge, especially when it is blood-stained [Table 2].

SYSTEMIC CAUSES FOR NIPPLE DISCHARGE:

Pathophysiological basis of the systemic causes: Any stimulation of thoracic nerves in the chest wall can cause a release of prolactin. Breast simulation, thoracic trauma, and herpes zoster are a few examples. Increased release of prolactin from the hypothalamic-pituitary axis due to hypothalamic damage, pituitary tumors, or the drugs affecting dopaminergic inhibition of prolactin can cause galactorrhea. High prolactin levels due to systemic causes such as hypothyroidism, Cushing, and other endocrine causes also cause nipple discharge. Cyclical causes of nipple discharge are based on hormonal fluctuations, and it changes depending on the days of the menstrual cycle. Usually, it's bilateral, copious, milky, and from multiple ducts.

Prolactin belongs to GH and the placental lactogen family as it shares common structural, functional, binding properties and common genetic ancestry[7]. Prolactin secretion is inhibited by dopamine, Gamma Amino Butyric Acid (GABA) & somatostatin, whereas it's promoted by Thyrotropin Releasing Hormone (TRH), opioids, oxytocin, serotonin, vasopressin, Vasoactive Intestinal Polypeptide (VIP), neurotensin, and galanin[8]. Prolactin has a role in stress as well, along with Adrenocorticotrophic Hormone (ACTH) and cortisol. It's also released from non-pituitary sites such as ovaries, endometrium, breast, lymphocytes, etc. It's metabolized in the liver and excreted through the kidneys [9, 10].

Etiologies of systemic diseases:

1. Pituitary-Hypothalamic causes: Microadenoma (<1cm) or macroadenomas (>1cm) of the pituitary is the commonest cause of pathologically high prolactin. They could be in isolation or part of syndromes such as Multiple Endocrinal Neoplasia (MEN-1) or Carney complex. Hypothalamic damage interrupts dopamine inhibition due to tumors, metastatic disease, stroke, infiltrative diseases, sarcoidosis, or Langerhans cell disease [11, 12].
2. Hypothyroidism also causes high prolactin due to high TRH. Polycystic Ovarian Syndrome (PCOS) can also cause high prolactin and galactorrhea. Renal failure, liver cirrhosis, causes high prolactin, but as the patients are usually sick and the reproductive system is suppressed, nipple discharge is not common [13, 14].
3. Pregnancy, Polycystic Ovarian Syndrome (PCOS), or other gynaecological causes are essential to exclude. Prolactin shares some structural and functional resemblance with placental lactogen.
4. Medications causing increased nipple discharge include antipsychotics (Phenothiazine), anti-emetic (metoclopramide), anti-depressants such as Tri cyclic anti-depressants (TCAs) or selective serotonin reuptake inhibitors (SSRI), a few anti-hypertensive drugs (methyldopa, atenolol), hormones including estrogen and progesterone. Drugs are reducing testosterone level or activity, such as danazol, cimetidine & opioids. Other drugs can affect the hypothalamic axis, including valproate, and drugs of abuse such as cannabis and Amphetamine. Medication-related nipple discharge is evident by history and the improvement when the culprit drug is stopped. First-generation Antipsychotics cause high prolactin more than second-generation drugs due to high Dopamine 2 Receptors (D2R) affinity. Aripiprazole, Olanzapine, and Quetiapine are second-generation with only a mild rise in prolactin and lesser galactorrhea[15] [Table 1].

Investigations for systemic causes: Prolactin level along with other pituitary hormones including Growth Hormone (GH), Thyroid function tests (TFTs), cortisol, and the blood tests for liver and kidney functions. Checking for other pituitary hormones is essential to exclude any co-secreting adenoma as many adenomas secrete prolactin and GH. Also, if there is macroadenoma, it can cause mass effect and hence deficiency of other pituitary hormones. Polycystic ovarian syndrome (PCOS) needs to be excluded, by pelvic scan and reproductive hormonal assessment, as it can also be one cause of nipple discharge. A pregnancy test is essential to make sure it's not due to placental lactogen. Macroprolactin should be excluded as macroprolactin is often not the cause of the discharge, even though the blood levels of prolactin are high. Macroprolactin is biologically not active unless it changes to a monomeric form. The drug list should be screened [16].

MRI Brain with Gadolinium is done to exclude adenoma. MRI Brain becomes especially important if there is no other reason for high prolactin or if there are focal symptoms and signs of pituitary-hypothalamic axis such as headache, visual

loss, raised intracranial pressure, or endocrinal changes suggestive of pituitary-hypothalamic disease. MRI Brain also is very helpful in patients who are on medications that can't be stopped, and we are not sure what was the baseline prolactin level before starting those medications. This is especially true for those on antipsychotics [17], [Table 2].

Management of systemic causes:

1. Pharmacotherapy: Microprolactinoma with no symptoms in a post-menopausal female doesn't require treatment. Dopamine agonists such as bromocriptine, cabergoline, quinagolide are first-line treatments for pathologically high prolactin. They also help reduce tumor size by apoptosis of lactotrophs. Bromocriptine is short-acting, needs a daily dose. Starting dose is 0.625mg to 1.25 mg / day. and the maximum dose is 15 mg/day. Cabergoline can be given once or twice a week, and the dose is 0.5-3.0 mg weekly. Quinagolide is a non-ergot D2R agonist with a once-a-day dose of 25 mcg OD, but the maximum can be 150 mcg/day. Cabergoline is the first choice due to its superior efficacy, convenience of dosing, and better side effect profile. Common side effects include nausea, vomiting, postural hypotension, Raynaud's, mood changes, psychosis, and extrapyramidal side effects. Currently, a screening echocardiogram should be done before stating Dopamine Agonists (DA) and then every 3-5 years to exclude any rare possibility of valvulopathy [18, 19]. Somatostatin analogues can also help control prolactin [20], [Table 2].
2. Surgery is an option for those who don't respond to drug therapy, macroadenoma with pressure effects, pituitary apoplexy, or young people who are not good candidates for lifelong treatment [21, 22].
3. Radiotherapy is the third option after medical and surgical causes[23].
4. Treat the underlying disease: Hypothyroid or chronic kidney disease (CKD) related high prolactin will settle when the underlying cause is treated. Drug-related high prolactin is best managed by stopping the drug when possible. Antipsychotics are not always easy to prevent or reduce the dose due to the risk of worsening of psychosis. Aripiprazole is a safer choice due to its partial agonist at D2R. Sex Hormone replacement is another option [24].

SUMMARY

Nipple discharge is a common presentation and is often due to local causes in the breast. Most important is to exclude any sinister reason, especially breast cancer. Through history, examination and testing are needed. Once local causes have been excluded, and the discharge is bilateral, milky, and coming from multiple ducts and is not serosanguinous, then a systemic search is needed. Drug history, assessment of pituitary-hypothalamic axis, thyroid functions, renal and hepatic functions are the main cornerstones of systemic assessment. Treatment depends on the cause. It can be managed by medications (dopamine agonists, somatostatin analogues, etc.) or surgery if it's prolactinoma. Treating hypothyroidism should normalize the prolactin. Pregnancy and lactation-related discharged or cyclical discharge often needs reassurance[25].

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