EPIDEMIOLOGY OF NIPPLE DISCHARGE

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SUMMARY

The Authors report their personal observations of nipple discharge in gynecologic patients admitted to the Obstetric and Gynecologic Department of Padua University or applying to the Senologic Diagnostic- or Endocrinology-Departments of the same.

After dividing breast secretions into two groups – the neuroendocrine and the strictly mammary ones – the Authors discuss their etiopathogenesis, incidence, and clinical significance (mainly as to their possible association to breast malignancies), and present their personal results.

At the end, a careful examination of all nipple discharges is recommended, which should include, besides cytological evaluation, a complete assessment of the neuroendocrine function and a watchful investigation of local breast conditions.

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The objective detection of mammary secretions is of great interest in mammary semeiotics. These secretions are currently divided into two wide groups, according to their different etiopathogenesis, age, incidence, therapeutical and physiopathologic implications, oncologic risk factors. The first group consists of galactorrheas. These secretions, of neuroendocrine genesis, are not physiologic, lacking an immediate relation to pregnancy or breastfeeding [1, 2]. They are characterized by bilateral, pluriorificial, whitish or milk-like (never hematic) mammary secretions.

The second group consists of serous, greenish, serosanguineous or hematic, often monolateral and monoorificial mammary secretions. Their pathogenesis is specifically mammary (fibrocystic mastopathy, intraductal papilloma, papillomatosis, carcinoma, etc.).

Let us examine the two groups: nipple discharge (first group) is a galactorrhea with two different possible pathogenetic sources: a) hyperprolactinemia with consequent anomalous hyperstimulation of the mammary receptor; b) overresponse by the mammary receptor in normoprolactinemia [2].

Galactorrhea is in both cases the epiphenomenon of many neuroendocrine physiopathologic factors that can today be more adequately studied thanks to the replacement of biologic prolactin assays [3, 4] by radioimmunologic assays [5, 6].

Hyperprolactinemia is generally the main cause of galactorrhea. It may origin from either a prolactin-secreting hypophyseal adenoma – prolactinoma – [7, 8, 9, 10, 11] or the suppression of the hypothalamus inhibiting activity due to a reduction of the prolactin inhibiting factor (PIF). PIF reduction may be caused by organic lesions in the central nervous system (traumas, inflammations, neoplasias), or by iatrogenic lesions due to pharmacologic interactions producing reduction of the dopaminergic tone or increasing the serotoninergic tone through various mecha-

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nisms ([7, 12, 13, 14, 15]). Dopaminergic - tone - reducing drugs include reserpine, methyldopa, chloropromazine, sulpiride and metoclopramide.

Imipramine and its derivatives increase the serotoninergic tone.

Oestrogens interact at hypothalamic level ([2]), stimulate the normal hypophysis to secrete prolactin ([6, 16, 17]) and promote mammary differentiation by their action synergic to prolactin. However, in high doses, they antagonize prolactin at mammary level thus inhibiting milk secretion ([2, 18]).

Galactorrhea following upon oestroprogestinic treatments is also noteworthy ([19, 20, 21]) for its influence on the hypothalamus cyclicity. Post-oestroprogestinic-pill amenorrhea (Shermann's syndrome) has a 0.9% overall incidence. However, in a selected group of 'risk-patients' with precedents of irregular menstruations, the incidence of amenorrhea with galactorrhea rises appreciably ([21, 24]).

The use of oral oestroprogestinics to 'regularize' menstrual cycles is therefore by no means advisable.

The high incidence of hypophyseal adenomas (20/23%) in cases of galactorrhea, 34% of the cases of amenorrhoic galactorrhea ([16]), demands accurate diagnoses.

Furthermore, the incidence of galactorrhea in menorrhoic patients (70% reporting regular cycles and 30% reporting irregular cycles) ([16, 24]) with prolactin within physiologic limits is likely to exceed the reported 30% because the poor symptomatology fails to alarm women.

Part of these galactorrheas, apparently idiopathic, develop towards positively hyperprolactinemic pictures, producing increasing menstrual irregularities or amenorrhea. Hypophyseal microadenomas are then detected.

These risk-patients should therefore undergo plasma prolactin RIA at least once a year and tomogram of the sella turcica ([16]) every 3/5 years.

From the epidemiologic point of view, the real incidence of galactorrhea is underestimated because many women do not regard it as pathologic, thus failing to turn to their doctors, unless it is associated with serious menstrual irregularities or amenorrhea ([16, 22, 23]).

The reported incidence therefore depends on the kind of examined patients, their health education and the pre-selection performed at different diagnostic moments. Our case-series report galactorrhea in 2.1% of all gynecologic patients, in 7.3% of the patients who turned to the Senology Diagnostic Department of our Institute and in 11.4% of the patients who turned to the Endocrinology Department. The pre-selection was clearly carried out according to the symptom importance.

The patients who apply to the Endocrinology Department usually present menstrual or other symptoms entailing psychologic involvement.

According to statistics, galactorrhea increases alongside with age. This might be associated with the decreasing physiologic activity of the mammary gland, due to the lower frequency of and longer intervals between pregnancies.

Mammary secretion was formerly almost permanent in women, due to their many and frequent pregnancies. Lower importance was therefore attached to galactorrhea than today, when spontaneous mammary secretion sometimes appears even in nulliparae.

The current increase in the incidence of galactorrhea can undoubtedly be explained by the increased use of psychotropic drugs and oestroprogestinics as well as by stricter semeiologic monitoring in malignant tumour prevention by specialized centres, or other factors involving patients themselves (breast-self examination).

Hence, greater chances to detect otherwise neglected galactorrheas ([1]).

The quantity of mammary secretion bears no relation to the nature or the

Table 1. — *Most frequent causes of galactorrhea (reported frequency in percent).*

	Authors	
	Kleinberg *et al.*	Tolis *et al.*
Pituitary tumors	20.4	23.4
Idiopathic with menses	32.3	27.6
Idiopathic with amenorr.	8.5	12.3
Chiari-Frommel	7.6	7.6
Tranquilizing drugs	6.8	9.2
Post oral contraceptives	5.1	13.8
Hypothyroidism	4.2	6.1
Empty sella	1.9	—
Miscellaneous	12.7	—

seriousness of the etiopathogenetic factors ([16, 21, 23, 24, 25]). A single patient can show mammary secretion of differing characteristics in subsequent examinations.

The reported mean incidence age ranges between 28.8 and 31.4 years ([16, 22, 23, 24]). Our case-series showed a 25.7 mean age. Therefore, the mean age in this group of nipple discharge patients is 25/30 years. The figure rises to 40/50 years in the group with specifically mammary pathogenesis. Table 1 shows – in percent – the interesting etiopathogenetic distribution of some case-series reported in the literature.

The anamnesis of galactorrhea patients reports weight losses, psychophysical stress, stigmata of hypothyroidism.

The 'galactorrhea-type' woman is under 30, thin, suffering from menstrual irregularities going as far as amenorrhea, may have previously used oestroprogestinics, has psychologic problems and is undergoing psychothropic therapy.

Recent studies ([26, 27, 28]) have furthermore suggested the existence of a relation beween mammary secretion in healthy, non-pregnant, adult women and the risk of mammary cancer.

Apparently, many chemical, nutritional, toxic and hormonal substances concentrate in the mammary liquid and remain in the ducto-alveolar system afterwards.

The importance of the mammary liquid secretion and absorbtion is thought to influence the mammary epithelium sensitivity to environmental carcinogen agents somehow reaching the circulatory system.

Galactorrhea is therefore an extremely important symptom and indication both for the frequently associated neuroendocrine pathologies and for these patients' potentially higher sensitivity to environmental carcinogenesis.

In nipple discharge due to more specifically mammary pathologies concerning the ductal secretory system (second group) pathologic secretions are almost always spontaneous ([29, 30, 31]). Table 2 shows the incidence of nipple discharge. Its frequency ranges from 3% to 9.6% ([29, 32, 33, 34, 35, 36]).

The differences between the various case-series stem from the use of varying selective criteria. For instance, Haagensen ([29]) excludes patients with recent pregnancies, use of oestroprogestinics, only induced secretion or affected by Paget's disease. This disease cannot be regarded as real nipple discharge because the liquid out flowing from the nipple eczematous lesion is exuded, not secreted. Paget's disease is characterized by nipple eczematous chronic lesions coupled with an underlying ductal carcinoma that appears at around 53/55 years ([29]). This disease accounts for 1.5% of all the cases of breast cancer. The liquid – hematic serum – is seldom a real secretion.

Table 2. — *Reported frequency of nipple discharge as the presenting symptom in different breast conditions.*

Authors	No. of patients	Percent	Total No. of patients
Haagensen	157	3.0	5233
McLaughlin & Coe	42	3.8	1082
Lewison & Chambers	114	5.2	2195
Hinchey	87	8.3	1051
Seltzer *et al.*	336	8.8	3787
Donnelly	218	9.6	2269

Table 3. — *Incidence of various types of nipple discharge (in percent).*

Authors	Bloody and sero-sang.	Serous	Watery	Milky	Miscel-laneous
Hinchey	54	22	3	7	14
Haagensen	49.7	49.7	0.6	—	—
Donnelly	55	21	—	6.0	17
Hendrick	34.8	7.8	—	11.2	46.2
Lewison & Chambers	47.4	28.9	7.0	9.9	6.8
Funderburk & Syphax	46.1	17.4	9.0	21	6.5
Madalin *et al.*	50	32			18

Table 4. — *Average age of patients complaining of nipple discharge.*

Authors	Mean age
McLaughlin & Coe	48.7
Madalin *et al.*	45.9
Copeland & Higgins	43.9
Haagensen	49.4
Hinchey	50

The secretion can be formed through two 'ductal' mechanisms. The first is simple, apocrine, epithelial desquamation, with stagnation in the ductal system. This first kind of epithelial desquamation is mainly produced by fibrocystic mastopathies and ductal ectasias. The secretion is often greenish-yellow.

The second mechanism consists of hyperplastic and neoplastic changes in the ductal epithelium ([36]).

Ductal proliferation (papilloma, papillomatosis, ductal carcinoma) is the pathogenetic origin of these cases. The secretion is mainly, though not necessarily, serous, serosanguineous or clearly hematic ([29, 30, 32, 33, 34, 35, 36, 37]).

No kind of secretion is specific or pathognomonic of a given mammary lesion and the same kind of mammary lesion can produce different secretions. Furthermore, the secretion characteristics may change in a single or in subsequent examinations in the same patient.

Table 3 shows the reported incidence rates of the various kind of secretions ([29, 30, 32, 33, 34, 36, 37, 38]).

The highest frequency is observed between the 4th and the 5th decades (tab. 4) ([29, 32, 34, 38, 40]).

The relation between the patient's age and the kind of secretion is thought to be more significant ([29, 32, 35, 40]).

Serosanguineous secretion is associated with papilloma in about 10% of the patients between the 3rd and the 4th decades; in about 18% of the patients in the 5th decade and in as much as 50% of the patients in the 7th decade ([30]).

Serosanguineous secretion may reveal carcinoma in 11.8% of the patients under

Table 5. — *Etiology of nipple discharge (reported frequency in percent).*

Authors	Cystic disease	Papil-loma	Carci-noma	Miscel-laneous
Donnelly	25	30	45	—
Hinchey	54	10	36	—
Haagensen	1.9	69	11.5	17.6
Campbell	24	36	38	—
Lewison & Chambers	40.3	23.7	19.3	17
Funderburk	32.5	35.5	7.3	24.7

Table 6. — *Reported incidence of carcinoma in patients with nipple discharge.*

Authors	Percent
Funderburk & Syphax	11.0
Haagensen	11.5
Mercier & Redon	11.6
McPherson & MacKenzie	12.5
Seltzer *et al.*	11.8 (<60 yrs) 32.0 (>60 yrs)
Lewison & Chambers	19.3
McLaughlin & Coe	26.1
Hinchey	36.0
Copeland & Higgins	37.0
Donnelly	45.0

Table 7. — *Reported frequency of nipple discharge in patients with breast carcinoma.*

Authors	No. of patients	Percent	Total No. of patients
Truscott *	59	7.5	787
Harnett *	56	2.2	2529
Hinchey	24	3.2	742
Treves	20	2.0	1000
Geschickter	96	4.0	2393

* Reported by Haagensen, in "Diseases of the breast", W. B. Saunders, Philadelphia, 1971, pp. 468-469.

60 and in 32% of those over 60 ([35]). Age is therefore a mere risk-parameter rather than an absolute criterion of seriousness.

Table 5 summarizes the main pathologies producing mammary secretion (intraductal papilloma, fibrocystic mastopathy and carcinoma) and their respective frequency in the literature ([29, 30, 33, 34, 36, 39]).

The differences between the various percentages are ascribable to the heterogeneous study-groups and the differing selective criteria.

In broader case-studies, differences also exist between the reported frequency of carcinoma in patients presenting secretion (tab. 6) ([29, 30, 31, 32, 33, 34, 35, 36, 40, 41, 42]). Mammary secretion is seldom a symptom of carcinoma ([29, 32, 43, 44]) as shown by the low percentage of correlation (tab. 7).

Nipple discharge must therefore be examined in relation to many other factors including the neuroendocrine function, the local situation, the associated pathology, the secretion characteristics and the patient's age.

Nipple discharge demands accurate diagnoses, relying on all the most advanced methods to examine mammary or hormonal conditions. This symptom – sometimes the only one to disclose even serious pathologies – must be given its full importance to help adequate and early interventions.

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