Radiological features of breast benign lesions in patients with hyperprolactinemia

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SUMMARY

Background: *The study was conducted to determine whether prolactin (PRL) influences radiological features of benign breast lesions.*

Methods: *During the 4-year period, we observed 50 patients with nipple discharge: 23 with normal serum prolactin levels (group 1) and 27 with hyperprolactinemia (group 2a before hyperprolactinemia treatment and group 2b after hyperprolactinemia treatment). Patients observed during this study underwent breast ultrasonography (US) and mammography. Radiological findings in group 1, group 2a and group 2b were compared.*

Results: *The most frequent radiological findings in group 2a were dilated lactiferous ducts and cystic lesions with statistical significances $p<0.001$ and $p<0.01$ in comparison to other radiological findings. In group 1 significantly less presence of dilated lactiferous ducts was observed ($p<0.05$) and proportional lower frequency of solid lumps compared to group 2a. Our results showed significantly lower incidence ($p<0.001$) of dilated lactiferous ducts, after hyperprolactinemia treatment (group 2b). In group 2b less presence of solid lumps and enlarged axillary lymph nodes is also observed in comparison to group 2a. Frequency of cystic lesions significantly decreased ($p<0.05$) and pseudocysts completely withdrew in patients with normalized serum prolactin levels.*

Conclusion: *Prolactin significantly influences radiological presentation of benign breast diseases. Treatment of hyperprolactinemia results in withdrawal of mammary duct ectasia, pseudocystic formations, cystic lesions and solid lumps. Breast ultrasonography and mammography should be considered as routine diagnostic procedures in patients with hyperprolactinemia.*

Key words: *Hyperprolactinemia; Ultrasonography, Mammary; Mammography; Breast Diseases; Mammary Glands, Human; Dilatation, Pathologic*

INTRODUCTION

Development and proliferation of mammary gland are to great extent hormone-dependent processes. Under synchronized effects of very complex neuroendocrine systems, normal breast tissue has ability to change morphological appearance. Prolactin is considered to be one of the most important inductors of mammary gland development, defined as mammopoesis, lactogenesis and involution (1). To respond to the biological requirements of the organism, mammary gland tissue integrates signals from extracellular matrix and hormonal stimulus from prolactin (2). Prolactin plays an important role in development of different benign breast lesions, including duct ectasia (3), fibrocystic breast disease (4), granulomatous mastitis (5) and chronic mastitis (6). A possible role of prolactin in mammary tumorigenesis has been the subject of considerable debate for many years. Even though great number of experimental and clinical studies supports the growth-promoting role of endocrine prolactin in mammary tumors, recent transgenic mouse models have revealed that over-expression of autocrine hPRL in a differentiating mammary gland induced dramatic functional and morphological defects, but not carcinoma (7).

Although breast cancer is the patient's biggest fear, more frequent disorder is benign breast disease. Up to 80% of the breast lesions are benign (8). Complex systemic hormonal and local factors are often responsible for the induction and/or maintenance of benign breast diseases (9).

Depending on the underlying breast pathology, different combination of diagnostic tests is used to establish the diagnosis and to help the physician in proper management planning. Breast ultrasonography and mammography are the most frequent procedures used in diagnosis and evaluation of breast lesions. Ultrasound has the ability to differ cystic lesion from solitary lump. This noninvasive diagnostic procedure also plays an important role in the detection of benign ductal disease both for the diagnosis and classification of focal masses and mammary-duct ectasia (10). Mammography is useful diagnostic procedure especially in: contralateral mammary gland follow-up, after surgery treatment; breast nodes evaluation, particularly in patients with numerous cystic lesions and patients with developed fibrolipomatous changes, in which other diagnostic procedures are less practicable.

This prospective clinical study was conducted with following aims: to establish main radiological features of breast lesions in patients with hyperprolactinemia and to determine whether prolactin normalization leads to alteration in radiological findings in breast tissue.

PATIENTS AND METHODS

During 4-year period (2004-2007) in Clinic for Endocrinology, diabetes and metabolic diseases, Clinical Center Nish, we observed 50 patients with nipple discharge: 23 with normal serum prolactin level (group 1) and 27 with hyperprolactinemia (group 2a before hyperprolactinemia treatment and group 2b after hyperprolactinemia treatment and normalization of serum prolactin levels).

Hormone assays

Serum PRL levels were assessed by RIA using commercial kits (IRMA hPRL, INEP Zemun-Belgrade, Serbia). The upper range of normal for serum PRL concentration was 650 ml U PRL/L in normal males and nonpregnant females.

Radiological procedures

Ultrasonography was done with „Sonoline Sienna", Siemens, with 7.5 MHz probe. In all 50 patients following breast ultrasound features were evaluated

and compared: the width of milk ducts, pseudocystic formation, cystic lesions, solid lumps, fibrocystic lesions, fibrolipomatosis, calcifications and enlarged axillary lymph nodes.

Mammography was done with „Mammomat", Siemens, using one-layer film mamoray HT „AGFA" 18x24, or laser film for daily unfolding AGFA or KODAK.

Statistical analysis

Distinctions in frequency of cytological parameters between clinical and control groups, were analyzed by χ^2 test. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

In our patients nipple discharge most frequently occurred between 31 and 40 of age, with no significant differences between patients with normal serum PRL levels and patients with hyperprolactinemia. Patients with hyperprolactinemia were significantly younger than patients from group 1 ($p < 0.05$).

Hormone assays results

PRL concentration

Twenty-three patients (46%) had normal serum PRL levels (group 1). In 27 patients (54%) serum PRL levels were above upper range of normal (group 2a). The highest PRL value was 4017.0 ml U/L and the lowest (but still above range of normal) was 664.0 ml U/L. Mean serum PRL levels were 1702.7 (926.81).

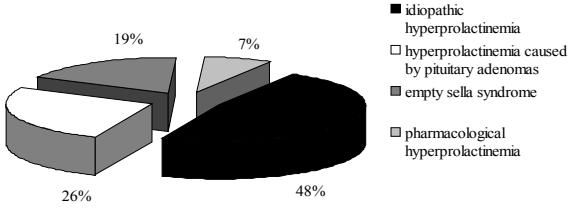

Figure 1. Etiology of hyperprolactinemia in group 2

Bromocriptine (BRC) therapy was administrated in 25 patients with hyperprolactinemia. Initial dose of BRC was 1.25 mg daily (in the evening hours). After each three days BRC dose was increased for 1.25 mg until normalization of serum PRL was achieved. None of the patients had severe side-effects (nausea, vomiting, headache, postural hypotension, or dizziness) which would demand stoppage of BRC treatment. Serum PRL levels were normalized in all 25 patients. After 2 months of treatment, dose adjustment was carried out on the basis of serum PRL suppression. Treatment was given at the maintenance dose to 3 patients for next 6 months, 14 patients for 12 months, and 8 patients for 24 months.

Radiological results

Breast ultrasonography

All 50 patients observed during this study underwent breast ultrasonography (US). Patients with hyperprolactinemia underwent US follow-up examination in period from 6 until 24 months, after serum prolactin levels were normalized. The most frequent US findings in group 2a of were dilated milk ducts and cystic lesions with statistical significances $p<0.001$ and $p<0.01$ in comparison to other US findings. In group 1 significantly less presence of dilated lactiferous ducts was observed ($p<0.05$) and proportional lower frequency of solid lumps compared to group 2a. Our results showed significantly decreased ($p<0,001$) number of patients with dilated lactiferous ducts after hyperprolactinemia treatment (2b). After serum PRL level normalization less presence of solid lumps and enlarged axillary lymph nodes is also observed in comparison to group 2a. Cystic lesions significantly decreased ($p<0.05$) and pseudocystic lesions completely withdrew in patients with normalized serum prolactin levels.

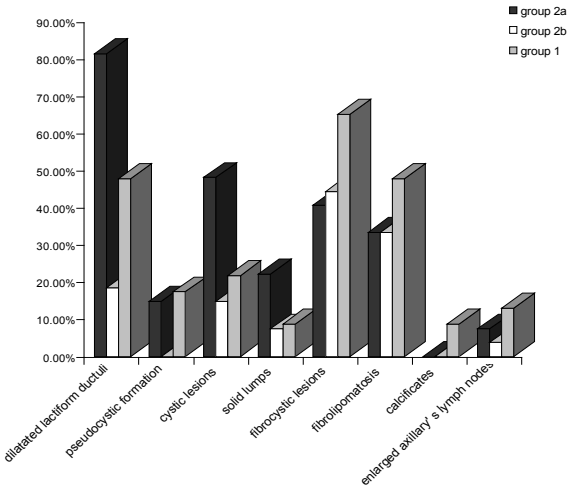

Figure 2. Frequency of breast ultrasound findings in group 1, 2a, and 2b

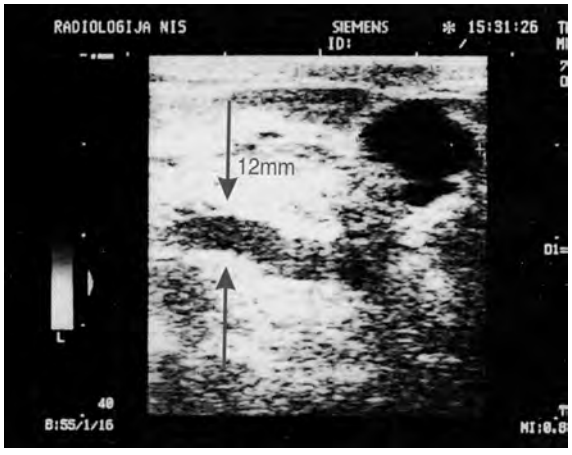

Figure 3. Dilated lactiferous ducts up to 12 mm, irregular, tortuous, with unequal luminary luminal width localized retromammilary in patient with hyperprolactinemia

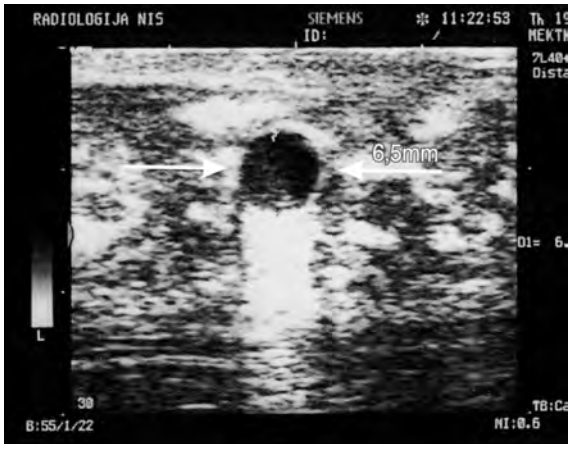

Figure 4. Retromammilary cystic lesion 6.5 mm in diameter with dense liquid content in patient with hyperprolactinemia

Mammography

Mammography was done in 8 patients. In group 1 mammography verified fibrocystic lesions in two patients and dominant vein blood vessels in two patients. None of group 1 patients had enlarged axillary lymph nodes. In group 2a mammography findings were similar: fibrocystic lesions in three patients and prominent vein blood vessels in one patient. Two patients had enlarged left axillary lymph nodes with diameter 10 to 11 mm.

DISCUSSION

Bromocriptine (BRC) therapy was started in 25 of 27 patients diagnosed with hyperprolactinemia. BRC was not administrated in remaining two patients with hyperprolactinemia because it was caused by Sulpirid therapy. After consultation with psychiatrist Sulpirid was stopped which resulted with serum PRL normalization. Despite BRC therapy, after 6 months, we verified increased serum PRL in 3 patients. Confirmed pregnancy was explanation for this, so further BRC treatment was stopped.

Our results showed a distinct positive correlation between hyperprolactinemia and dilated lactiferous ducts which confirms important prolactin role in this US finding. It is well known that hyperprolactinemia increases milk synthesis followed by milk stasis and dilation of milk canals. Dilated milk canals, in short time, become full of granulated, necrotic and acidic detritus, which mainly contain macrophages full of lipids. Collected debris causes sterile ductal inflammation. Increased milk synthesis, milk stasis and intraductal inflammation will be followed by leakage of glandular secretion through the wall of the ducts and spreading of intraductal inflammation to periductal space (3,5,6). Significantly decreased number of patients with dilated lactiferous ducts, after serum PRL level normalization ($p<0.001$) once again confirms important role of hyperprolactinemia in mammary duct ectasia and points out that dilatation of mammary ducts is reversible process.

Major duct ectasia spreads centrifugally following a segmental pattern through the breast. It is necessary to perform radial US scans around nipple to detect presence of mammary duct ectasia. US enable visualization of simple and pseudocystic mammary-duct ectasia (10). Our results showed that after hyperprolactinemia treatment none of the patients had pseudocystic lesion. Normalization of serum PRL levels leads to decreased milk synthesis and milk stasis. Intraductal and periductal inflammation also start to withdraw. Dilatation of lactiform ductuli decreases which is followed with decreased pseudocystic lesions in the breast.

Number of patients with cystic lesions from group 2a was higher in comparison with group 1, but without statistical significance. The present findings could support hypothesis that cystic lesions have multifactorial genesis in which hyperprolactinemia has a certain role. Our results also verified that number of patients with cystic lesion significantly decreased after hyperprolactinemia treatment. These results lead to conclusion that mammary duct ectasia, pseudocystic formations and cystic lesions could be different stages of the same pathological process which starts with hyperprolactinemia. Once started pathological changes of lactiform ductuli in one point loose reversibility, so normalization of serum PRL levels is not followed with complete withdrawal of cystic lesions.

Prolactin plays an important role in the proliferation and differentiation of normal breast epithelium. The effects of prolactin are mediated by its receptor. Alteration in the expression of this receptor could be important for development of benign and malignant breast diseases. Some studies results pointed out that correlation between higher expression of PRL receptor and fibroadenomas could be an important factor in the pathogenesis of these disease (11). In our study among patients from group 1, frequency of solid lumps was significantly smaller in comparison with other US findings. We observed decreased number of patients with solid lumps after hyperprolactinemia treatment (group 2b). In a few patients remaining solid lumps had smaller diameter. The present findings support hypothesis that hyperprolactinemia influences pathogenesis and maintains of solid lumps.

Even though there are data in the literature which support correlation between hyperprolactinemia and fibrocystic breast disease (4) our study results did not confirm that hypothesis. We verified higher percentage of fibrocystic lesions in group 1. Reason for this could be a fact that patients from group 1 were significantly older in comparison to patients with hyperprolactinemia. It is already mentioned that hyperprolactinemia increases milk synthesis, followed by milk stasis which could promote intraductal and periductal inflammation (3,5,6). Fibroblastic proliferation is increased in order to overcome inflammatory process in breast tissue. This could explain slightly increased number of patients with fibrosis observed after normalization of serum PRL levels.

Our results verified higher percentage of fibrolipomatosis in group 1. These patients were significantly older in comparison to patients with hyperprolactinemia. Involution process in breast tissue usually starts in menopausal women. This process is slow, but continuous. The main features of these involution changes are ductal atrophy followed by interlobular stromal shrinking. Blood and lymph vessels also become smaller. Brest lobular pattern is lost. Fat accumulates instead of glandular tissue which starts to „vanish". We noticed that normalization of serum PRL levels had a little influence on irreversible process of fibrolipomatosis.

The most calcifications in the mammary gland are associated with benign breast disease. The latest study attempts to standardize the procedure of correlating histological findings with radiological detectable calcification (12). In our study only a few patients had this US finding. All of them had calcifications associated with benign breast disease.

Enlarged axillary lymph nodes can be a part of clinical findings in nonpuerperal mastitis. In very few patients from group 2a US verified enlarged axillary lymph nodes. This finding could be explained as reaction to inflammatory process (intraductal and periductal inflammation) in breast tissue. Normalization of serum PRL levels is followed by decreased intraductal and periductal inflammation. None of the patients after hyperprolactinemia treatment had enlarged axillary lymph nodes on the control US.

There were no significant differences in mammography findings between patients from group 1 and 2a. All mammograms confirmed presence of normal cutis and subcutis and normal nipple and mammary gland.

CONCLUSION

Prolactin significantly influences radiological presentation of benign breast diseases. Ultrasound findings show that hyperprolactinemia treatment results in withdrawal of mammary duct ectasia, pseudocystic formations, cystic lesions and solid lumps. Breast ultrasonography and mammography should be considered as routine diagnostic procedures in patients with hyperprolactinemia.

Conflict of interest
We declare no conflict of interest.

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