

PREVALENCE AND CLINICAL SIGNIFICANCE OF HOOK-EFFECT AND MACROPROLACTINAEMIA PHENOMENONS IN PATIENTS WITH PROLACTINOMAS



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Introduction

More than 85% of circulating prolactin (PRL) is presented by monomeric form (23.5 kDa), consisting of 199 amino acid. Serum also contains a covalent bind complex of low-molecular PRL and PRL-binding protein, "big prolactin", with low biological activity. The third PRL form is a much larger polymeric form, "big prolactin" (150-170 kDa), generally presented by a complex of low-molecular PRL and immunoglobulin G (IgG) which is currently defined as macroprolactin. Mechanisms involved in the development of such complex are still unknown, and it is supposed that pathological autoimmune mechanisms lie at the heart of the process.

Macroprolactinemia

Commercial assays can not separate macroprolactin from the whole pool of hormone. That's why additional methods for macroprolactin identification had been developed: gel filtration chromatography of the serum, treatment of serum with polyethylene glycol (PEG), anti-human immunoglobulin G, and protein A antibodies. Retrospective analysis of patients with hyperprolactinemia showed that approximately 10-40% of them had macroprolactinemia, but the real incidence of this phenomenon is still unknown. Due to low biological activity of polymeric PRL form just small proportions of patients with macroprolactinemia has signs and symptoms of hyperprolactinemia. Galactorrhea presents in 20%, oligo/amenorrhea in 45% of cases. Only in 20% of patients with macroprolactinemia pituitary adenomas were identified. That's why macroprolactin value should be determined in order to make a decision whether dopamine agonist's therapy is necessary or not. More over at the beginning of drug therapy the dosage of medicine should be based on the level of monomeric PRL, instead of the general hormone maintenance.

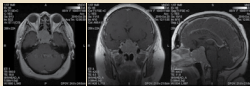
Hook-effect phenomenon

For the majority of prolactinomas, serum PRL levels directly associated with tumor size. In some cases tumor mass and PRL rate may be dissociated. One potential reason of such discrepancy is the hook-effect — an assay artifact that may be observed when high serum PRL concentrations saturate antibodies in the two-site immunometric assay. Therefore, false low results may be obtained.

Presence of hook-effect phenomenon should be suspected when macroadenoma with the vivid symptoms of hyperprolactinemia and moderate elevation of PRL level is identified. In order to exclude a potential hook-effect, the assay should be repeated after a 1:100 serum sample dilution. This step allows excluding an incorrect conclusion about existence of large nonfunctioning adenoma with pituitary stalk compression and dopaminergic neuronal damage. As a result unnecessary surgery could be avoided.

Objective

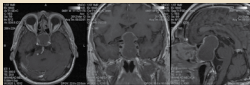
To assess the prevalence and clinical significance of such laboratory phenomenon as hook-effect and macroprolactinemia in patients with hyperprolactinemia.



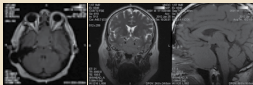
MRI of giant prolactin-secreting pituitary adenoma



CT 3D reconstruction of destroyed sella turcica



MRI of large prolactin-secreting pituitary adenoma



MRI of giant prolactin-secreting pituitary adenoma

Materials and methods:

For macroprolactinemia phenomenon screening total of 219 patients with increased PRL level without pronounced hyperprolactinemia symptoms was included in research. Among them 94 patients with prolactinomas and 162 patients with physiological, pharmacological and pathological non-tumoral hyperprolactinemia.

For an assessment of hook-effect phenomenon 117 patients with macroadenomas and vivid symptoms of hyperprolactinemia against moderate increase of the PRL level were investigated.

Patients were examined using generally accepted (conventional) laboratory and instrumental methods of diagnostics: MRI and CT of a brain with contrast enhancement (MRI Signa Horizon 1.5 T HDs (GE Medical Systems, LLC, USA), CT Aquilion 64 (Toshiba Medical Systems Corporation, Japan)), standard commercial sets for immunochromatometric analysis. Macroprolactin identification was made by treatment of sera with polyethylene glycol (PEG). According to size the pituitary adenomas were classified as microadenomas, with their diameter less than 10 mm, macroadenomas — from 10 to 20 mm, macroadenomas — from 20 to 40 mm, giant adenomas — more than 40 mm in diameter. Neurophysiological inspection included an estimation of visual acuity, a condition of an eye ground, function of oculomotor nerves, color parietry.

Results and discussion:

Macroprolactin was investigated in 94 cases (34%) of prolactinomas (69 women (73%) and 25 men (27%) with asymptomatic hyperprolactinemia. If a preponderance of polymer forms more than 60% was obtained, the macroprolactinemia phenomenon was stated. Phenomenon of macroprolactinemia was found in 17 patients (18%) with macroadenomas, and was negative in patients with other tumor sizes ($p < 0.01$). A total level of PRL varied from 1522 mIU/l to 10040 mIU/l. Average content of PRL in those patients was 1550 ± 1.7 mIU/L. Average content of macroprolactin was $64.5 \pm 4\%$.

As macroprolactinemia is a common cause of hyperprolactinemia in women with macroprolactinemia without initial neurological symptoms and pure clinical syndrome, it can become the reason of hypogonadism of a disease.

To make a decision if the patients need dopamine agonist's complex investigation including an assessment of a hypogonadism and the metabolic violations caused by hyperprolactinemia should be performed. If dopamine agonist's therapy is necessary, the dose of preparations should be selected, according to level of biologically active monomeric PRL fraction. It should be done to prevent hyperprolactinemia, which also negatively influence on reproductive function.

Macroprolactin was checked-out in 162 cases of non-tumoral hyperprolactinemia (142 women (87%) and 20 men (13%)). Phenomenon of macroprolactinemia was revealed in 40 cases (25%). A total level of PRL varied from 724 mIU/l to 5633 mIU/L. Average content of PRL in those patients was 1696.8 ± 1.3 mIU/L. Average content of macroprolactin was $75 \pm 8\%$.

Macroprolactinemia is a very common reason of high serum PRL levels at patients with non-tumoral hyperprolactinemia. That's why we suggest screening for macroprolactin in patients with moderate hyperprolactinemia to avoid unnecessary further investigations and dopamine agonist's therapy.

If discrepancy between very large pituitary tumor and a mildly elevated PRL level in untreated patients with pronounced clinical features of hyperprolactinemia appeared hook-effect phenomenon was excluded. In order to eliminate a falsely understating of PRL level serial dilutions (1:100) of serum samples in 117 patients were performed.

Hook-effect phenomenon in our study was established in 6 patients (6.2%) with macroprolactinomas and gives an increase of PRL level from 1500 to 21,390 mIU/l, from 3180 to 130,785 mIU/l and from 4200 to 240,168 mIU/l, from 900 to 24000 mIU/l, from 1500 to 37000 mIU/l, from 328 to 5700 mIU/l.

Because hook-effect cannot be reliably distinguished on clinical criteria alone, we recommend 1:100 serum sample dilution in patients who have pituitary macroadenomas and apparently normal or mildly elevated PRL levels to overcome this phenomenon.

It should be noted that hook-effect is not constant. In the biochemical hook-effect phenomenon — here underlies a deformation of immunochromatometric analysis results due to extremely high serum PRL concentration. We recommend to perform serum sample dilution (1:100) during the prolactinomas treatment used hook-effect disappearance once in study. Note to state that further serum dilutions will not reflect a true hormone concentration. It's only a mathematical result of hormone concentration to dilution grade. The tumor thinking seen on MRI is another criteria of treatment efficiency in addition to decrease of PRL level.

Conclusion

As phenomenon of macroprolactinemia and hook-effect cannot be reliably distinguished on clinical criteria alone, we recommend routine screening for macroprolactin in patients with asymptomatic macroprolactinomas and patients with non-tumoral etiology of hyperprolactinemia, and hook-effect exclusion by serum dilution in patients with macroadenomas in order to avoid misdiagnosis and mismanagement.

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