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Prolactinoma and cardiovascular diseases – an interdisciplinary problem

Prolaktynoma a choroby układu sercowo-naczyniowego – problem interdyscyplinarny

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Abstract

Prolactin-secreting pituitary tumour is a rare disease, in which excess prolactin causes significant functional and constitutional disorders of the whole body. Hyperprolactinaemia is associated with changes in body composition and metabolic disorders. The long-term prognosis and quality of life in patients with prolactinoma are mainly influenced by cardiovascular disorders, which, if left untreated, increase the cardiovascular risk and limit the treatment options for secondary organ complications. Cardiovascular mortality in patients with prolactinoma is several times higher than in the general population. Early diagnosis of prolactin-releasing pituitary tumour and a thorough morphological and functional cardiovascular assessment at each stage of the disease are necessary for risk stratification. Patients with prolactinoma should be put on combined treatment based on both serum prolactin control, and reduction of cardiovascular risk factors. Normalisation of prolactin levels and reduction of the tumour mass, achieved mainly through effective pharmacotherapy, reduce mortality and the risk of cardiovascular complications; therefore, the earliest possible diagnosis of prolactin pituitary tumour and implementation of appropriate treatment as well as active diagnosis and therapy of coexisting organ complications should be set as a goal in these patients. It seems that a thorough cardiological assessment of patients with prolactinoma should be obligatory, regardless of their age or the time of diagnosis. The aim of this study was to present the complexity of clinical problems in patients with prolactin-secreting pituitary tumours, who require special interdisciplinary care.

Keywords: prolactinoma, cardiovascular diseases, hypertension

Streszczenie

Guz prolaktynowy przysadki jest chorobą rzadką, w której pod wpływem nadmiaru prolaktyny dochodzi do istotnych zaburzeń funkcjonalnych i konstytucjonalnych całego organizmu. Hiperprolaktynemia jest związana ze zmianami w składzie ciała i zaburzeniami metabolicznymi. Na rokowanie odległe i jakość życia u chorych z prolaktynomą szczególnie wpływ mają przede wszystkim zaburzenia układu krążenia, które nieleczone zwiększają ryzyko sercowo-naczyniowe i ograniczają możliwości terapii wtórnych powikłań narządowych. Śmiertelność z powodu chorób układu sercowo-naczyniowego u chorych z prolaktynomą jest kilkakrotnie większa niż w populacji ogólnej. Wczesne rozpoznanie guza prolaktynowego przysadki oraz dokładna ocena morfologiczna i czynnościowa układu krążenia na każdym etapie choroby są konieczne w celu stratyfikacji ryzyka. Leczenie chorych z prolaktynomą powinno być skojarzone i opierać się nie tylko na kontroli stężenia prolaktyny w surowicy, ale również na redukcji czynników ryzyka sercowo-naczyniowego. Normalizacja stężenia prolaktyny i redukcja masy guza, osiągnięte przede wszystkim poprzez skuteczną farmakoterapię, zmniejszają śmiertelność i ryzyko powikłań ze strony układu sercowo-naczyniowego, należy więc dążyć do jak najwcześniejszego rozpoznania guza prolaktynowego przysadki i wdrożenia odpowiedniego leczenia oraz aktywnej diagnostyki i terapii współistniejących powikłań narządowych. Wydaje się więc, że rzetelna ocena kardiologiczna chorych z prolaktynomą powinna być obowiązkowa, niezależnie od ich wieku i czasu rozpoznania choroby. Celem niniejszej pracy było przedstawienie złożoności problemów klinicznych występujących u pacjentów z guzem prolaktynowym przysadki, którzy wymagają szczególnej opieki interdyscyplinarnej.

Słowa kluczowe: prolaktynoma, choroby układu sercowo-naczyniowego, nadciśnienie tętnicze

INTRODUCTION

Prolactinoma is the most common pituitary adenoma. The excess of autonomously secreted prolactin in both women and men leads to hypogonadism, which is manifested by e.g. reduced libido, menstrual disorders in women, impotence in men, as well as infertility, galactorrhoea and decreased bone mineral density. Clinical symptoms depend on tumour size and the severity of hyperprolactinaemia⁽¹⁾.

EPIDEMIOLOGY

The prevalence of prolactinoma is estimated to be approximately 30 per 100,000 in women and 10 per 100,000 in men. The mean annual prevalence is estimated at 6 per 100,000. The median age at diagnosis is 31–32 years for women and 39–48 years for men^(1–3).

Data on the incidence of cardiovascular diseases in the group of patients with prolactinoma are sparse, but indicate an increased cardiovascular risk and mortality, mainly due to overlapping metabolic disorders and premature atherosclerosis^(4–9). This is related not only to the overproduction of prolactin itself, but also to its negative effects on the activity of the hypothalamic-pituitary-gonadal axis. Decreased libido is the first symptom of these disorders; additionally, ovulation disorders, followed by prolonged menstrual cycle, and secondary amenorrhea may occur in women, while hypogonadism leading to impotence and metabolic complications may develop in men⁽⁵⁾. The complex pathomechanisms that may contribute to cardiovascular complications in patients with prolactinoma include vascular endothelium dysfunction with altered peripheral vascular resistance, overlapping metabolic disorders, insulin resistance syndrome, as well as lipid metabolism disorders^(6–10). The most common cardiovascular abnormalities in patients with prolactinoma include left ventricular dysfunction, hypertension, arrhythmias, valvular heart disease, vascular endothelial dysfunction, hyperinsulinaemia, lipid metabolism disorders^(6,7,10–12).

LEFT VENTRICULAR DYSFUNCTION

Hyperprolactinaemia in patients with prolactin-secreting pituitary tumours is associated with vascular endothelial dysfunction and multiple overlapping cardiovascular risk factors, and therefore may lead to myocardial dysfunction. Research shows that untreated prolactinoma patients develop subclinical myocardial dysfunction, which is characterised by left ventricular systolic and diastolic dysfunction, confirmed by tissue Doppler echocardiography⁽¹²⁾. Increasing research is currently focused on demonstrating a direct causal relationship between prolactin levels and cardiovascular diseases⁽¹³⁾. Hyperprolactinaemia was diagnosed in 25% of patients with heart failure⁽¹⁴⁾. Under oxidative stress conditions, prolactin can be metabolised to

a shorter form with a molecular weight of 16 kDa, which has a strong cardiotoxic effect, inhibits the proliferation and migration of endothelial cells, promotes vasoconstriction and causes cardiomyocyte dysfunction, ultimately leading to heart failure and increased mortality⁽¹⁵⁾. Studies have confirmed that this shorter form contributes to postpartum cardiomyopathy during periods of increased oxidative stress caused by pregnancy⁽¹⁶⁾. Based on these findings, it can be assumed that blocking prolactin release with bromocriptine may prevent postpartum cardiomyopathy⁽¹⁷⁾. The relationship between serum prolactin levels and myocardial remodelling was also observed in men⁽¹⁸⁾. Furthermore, it has been shown that hyperprolactinaemia is more often associated with classic cardiovascular risk factors, such as increased body weight, insulin resistance, and lipid disorders^(7,19). At the same time, hyperprolactinaemia is associated with an inflammatory response and higher C-reactive protein (CRP) in a the high-sensitivity CRP (hs-CRP) test, which is also a risk factor for cardiovascular complications⁽²⁰⁾. Additionally, prolactin may play an important role in the development of atherosclerosis, affecting arterial stiffness and compliance. Hyperprolactinaemia has also been shown to be associated with vascular endothelial dysfunction and aortic stiffness⁽²¹⁾. It cannot be ruled out that left ventricular systolic and diastolic subclinical dysfunctions are induced by classical and non-classical cardiovascular risk factors correlated with the presence of a prolactin pituitary tumour rather than with increased serum prolactin alone⁽¹²⁾.

HYPERTENSION

Hypertension (HT) is a common problem in the population of patients with prolactin-secreting pituitary tumours, and its course varies considerably. The disease develops early and may persist for several years after achieving remission of the underlying disease⁽²²⁾. The pathogenesis of hypertension in this case is multifactorial, i.e. patients develop secondary HT promoted by concomitant metabolic disorders⁽⁴⁾. It may be difficult to control HT in this group of patients, and the current guidelines emphasise the need for personalised antihypertensive therapy. The treatment of patients with prolactinoma should be combined and focused not only on the normalisation of serum prolactin levels, but also on the reduction of cardiovascular risk factors^(1,8).

VALVULAR HEART DISEASE

Long-term therapy with dopamine agonists is associated with an increased incidence of structural abnormalities and calcifications within the heart valves, leading to asymptomatic valvular disease^(23,24). Tricuspid valve regurgitation (usually asymptomatic) is common in patients with prolactinoma treated with cabergoline⁽²¹⁾. Considering the potential risk of heart defects in patients with prolactinoma treated with dopamine agonists (bromocriptine, cabergoline),

tricuspid, mitral, aortic and pulmonary valvular insufficiency in particular, regular cardiological screening, including echocardiography, is recommended in these patients⁽²⁴⁾.

VASCULAR DISEASE

Secondary endothelial dysfunction leading to vasoconstriction impairment plays an important role in the development of cardiovascular disorders in patients with prolactinoma. It was shown that prolactinoma patients present with a hypercoagulable state, which is characterised by high platelet counts, high levels of fibrinogen and plasminogen activator inhibitor-1, decreased activity of plasma tissue factor pathway inhibitors, as well as increased levels of total cholesterol, low-density lipoproteins (LDL) and apolipoproteins B⁽⁹⁾. Studies have shown that hyperprolactinaemia is associated with increased levels of inflammatory biomarkers, including interleukin-6, an unfavourable cardiovascular risk profile and increased cardiovascular mortality^(9,25,26). Metabolic disorders and hypercoagulability are predictors of preclinical atherosclerosis in this group of patients^(3,6–8,22,27). Furthermore, the high level of expression of prolactin receptors in atherosclerotic plaques suggests that prolactin could modulate the atherosclerotic process. The role of prolactin receptor-triggered signalling in promoting atherosclerosis corresponds to previous *in vitro* studies showing that prolactin can modulate inflammatory responses, stimulate mononuclear cell adhesion to the endothelium, and promote smooth muscle cell proliferation in the vessels⁽¹¹⁾.

PROLACTINOMA-RELATED ABNORMALITIES IN MEN

Mortality in men with prolactinoma is several times higher than in the general population, mainly due to cardiovascular complications^(4,5). It is worth noting that the diagnostic delay in prolactinoma ranges from 6 months to 12 years, which means a relatively long time of exposure to elevated serum prolactin⁽³⁾. Since men with prolactinoma are diagnosed at an older age than women, possibly due to delayed medical appointment or diagnosis, they may be at a greater risk of the consequences of chronic hyperprolactinaemia and related hypogonadism⁽³⁾. The duration of exposure to excess prolactin may be a significant factor in the development of cardiovascular complications. Long-term hyperprolactinaemia and its consequences, as well as hypopituitarism and its treatment may be the mechanisms underlying the higher incidence of cardiovascular complications in this group of patients^(3,28).

METABOLIC DISORDERS

It has been found that hyperprolactinaemia is associated with weight gain, regardless of its aetiology^(29,30). Weight gain secondary to hyperprolactinaemia is believed to be

associated with altered appetite and satiety regulatory systems^(31,32).

Hyperprolactinaemia is associated with impaired glucose homeostasis and decreased tissue insulin sensitivity. This is due to the effect of prolactin on the growth of pancreatic islet cells and insulin production^(7,33). Patients with prolactinoma have been shown to have higher fasting glucose compared to age, sex and weight-matched controls, suggesting that the diabetogenic effect of prolactin may be independent of its effect on body weight.

Hyperprolactinaemia has been shown to be associated with lipid disorders, such as increased LDL, triglycerides, and decreased high-density lipoproteins (HDL). The abnormal lipid profile in patients with hyperprolactinaemia is partly due to weight gain and partly due to the lipogenic effect of prolactin⁽³⁴⁾. This may be due to a decreased activity of lipoprotein lipase in fat cells, leading to disorders of lipid metabolism and the development of adipose tissue⁽³⁵⁾. It has been documented that patients with prolactinoma have higher levels of LDL cholesterol and triglycerides compared to age, sex, and weight-matched controls. Other studies documented low HDL cholesterol, although there were no differences in serum triglyceride or LDL cholesterol levels⁽³⁶⁾. It has been confirmed that the levels of total cholesterol and LDL cholesterol are higher in women with amenorrhoea accompanied by hyperprolactinaemia compared to an age-matched control group⁽³⁷⁾.

RESPIRATORY DISORDERS

The prevalence of sleep disordered breathing, including obstructive sleep apnoea has not been sufficiently documented in patients with prolactinoma. Considering the fact that obesity is one of the main risk factors for obstructive sleep apnoea, it can be concluded that sleep disordered breathing is very common in patients with prolactinoma. The incidence of obstructive sleep apnoea in patients with prolactinoma is similar to that in obese patients and does not change after treatment with dopamine agonists. Higher body mass index (BMI) and visceral obesity appear to be the major risk factors for sleep disordered breathing in patients with prolactinoma⁽³⁸⁾.

CARDIOVASCULAR PREVENTION AND TREATMENT

The main therapeutic goals in a prolactin-secreting pituitary tumour are to reduce the tumour mass, normalise prolactin levels and restore normal gonadal function. This leads to the resolution of menstrual disorders and galactorrhoea in women, improved male potency, restoration of libido and fertility, reduced risk of osteoporosis secondary to chronic hypogonadism, as well as reduced risk of cardiovascular complications and death. Dopamine receptor agonists are the treatment of choice. In most patients, chronic dopaminergic therapy leads to inhibition of prolactin secretion

and tumour regression (even by >50% in 90% of patients after one year). Treatment usually lasts for many years, with continuous dopaminergic therapy needed to achieve remission. It is recommended to perform a follow-up magnetic resonance imaging (MRI) to assess prolactin-releasing pituitary tumours after one year of pharmacotherapy; however, MRI should be performed after 3 months in the case of pituitary macroadenomas without biochemical and neurological improvement. Discontinuation of conservative treatment usually leads to tumour progression. Only patients who are refractory (10% of patients) or intolerant (10%) to pharmacotherapy are treated surgically. Surgical outcomes depend on the size and location of the pituitary tumour. Neurosurgical treatment of large, invasive macroadenomas is usually incomplete and ineffective, and has a high complication rate. In the case of microprolactinoma, the postoperative remission rate and the risk of recurrence are 70% and 20%, respectively. The same values are 38% and 50%, respectively, for macroprolactinoma. The 10-year risk of progression from microadenoma to macroadenoma is 7%. Large tumours producing neurological symptoms respond well to pharmacotherapy in 90% of cases⁽¹⁾. Treatment with a dopamine receptor agonist may lead to weight loss and improved metabolic parameters. After 6 months of treatment with dopamine analogues, a significant decrease in insulin resistance, fasting glucose levels, as well as normalisation of LDL cholesterol and triglyceride levels were observed. However, there was no significant difference in BMI⁽³⁹⁾. Perhaps longer duration of therapy is needed to confirm the beneficial effects of dopamine analogues on body weight and BMI in patients with prolactinoma. These patients should be put on combined treatment that will not only control serum prolactin levels, but also reduce cardiovascular risk factors⁽⁸⁾. There are ongoing studies assessing the effects of dopamine agonists on body weight and other metabolic parameters in patients with hyperprolactinaemia^(7,40). Many studies have already confirmed that treatment with dopamine agonists induces weight loss^(31,32,39). The effect of therapy with dopamine agonists on body weight appears to be sex-dependent. Recent studies have shown that reduced body weight and BMI after treatment with this class of drugs is either observed only in men or much more pronounced in men than in women^(29,30). However, another study, in which females predominated, also documented a significant reduction in body weight after 3 months and a further reduction in body weight after 6 months of cabergoline treatment, with significantly reduced BMI and body fat, indicating that the effects of dopamine agonists on body weight may also occur in women⁽⁶⁾. Reduction of body weight and abdominal obesity with dopamine agonists is noticeable already after 3 months and may last for up to 5 years⁽²⁹⁾. There is evidence that tissue sensitivity to insulin improves after 6 months of treatment with cabergoline, as evidenced by reduced HOMA-IR (homeostatic model assessment – insulin resistance) index^(20,41). Improved tissue insulin sensitivity was observed in hyperprolactinaemic patients treated

with dopamine agonists, and this effect was independent of body weight changes^(40,41).

Studies also documented a significant reduction in LDL-cholesterol and triglycerides after 3 months of cabergoline therapy, with a further decrease after 6 months and a significant reduction in total cholesterol after 6 months of treatment⁽⁶⁾. Many studies have shown an improved lipid profile after treatment with dopamine agonists. The observed improvement may occur already after 2 months and last up to 5 years after treatment onset⁽⁷⁾. Changes in lipid parameters become noticeable long before changes in body weight, suggesting that the improvement may be due to the direct action of dopamine agonists rather than body weight. Continuous improvement of lipid parameters was also demonstrated when using higher doses of cabergoline, even after 12 months of treatment⁽⁴²⁾.

CONCLUSIONS

The uncontrollable course of prolactinoma due to prolonged tissue exposure to excess prolactin may be associated with an increased incidence of serious morphological and functional cardiovascular abnormalities. Early diagnosis and rapid initiation of treatment of prolactinoma to control biochemical parameters and reduce tumour mass-related complications is the best strategy to prevent cardiovascular complications. Patients with prolactinoma require interdisciplinary treatment and care with the use of modern diagnostic tools that allow for identifying subclinical systemic complications.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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