Diabetes insipidus and other symptoms in patients with pituitary metastases – a genuine or a casuistic problem? How to improve quality of life and optimize patient care?

Moczówka prosta i inne objawy w przebiegu przerzutów nowotworowych do przysadki mózgowej – realny problem czy kazuistyka? Jak poprawić jakość życia chorych oraz pomóc w optymalizacji opieki nad pacjentami?

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Nowotwory złośliwe stają się poważnym zagrożeniem dla zdrowia i życia populacji na całym świecie. Chociaż przysadka mózgowa nie jest częstą lokalizacją ognisk metastatycznych, w ciągu ostatnich kilku dekad zauważa się wzrost rozpoznawania zmian w tej lokalizacji. 2/3 z nich stanowią przerzuty raka płuc i raka piersi. Celem pracy jest przedstawienie epidemiologii, objawów klinicznych (w tym moczówki prostej jako najczęstszej manifestacji) przerzutów nowotworowych do przysadki, a także postępowania i rokowania. Przerzuty nowotworowe do przysadki mózgowej są zwykle bezobjawowe i mogą pojawić się w różnym okresie choroby nowotworowej lub być nawet jej pierwszym objawem. Przysadka może być także jedynym miejscem ich lokalizacji. Częściej występują w płacie tylnym niż przednim. W przypadku obecności objawów klinicznych, moczówka prosta jest najczęstszą, a czasem pierwszą manifestacją choroby nowotworowej. Hiperprolaktynemia i niedoczynność płata przedniego (maskowana przez powikłania ogólnoustrojowe choroby nowotworowej) zdarzają się nieco rzadziej. Objawy kliniczne, zmiany w MR oraz wywiad obciążony chorobą nowotworową są pomocne we wstępnej diagnozie, ale ostateczne rozpoznanie może być postawione wyłącznie po uzyskaniu wyniku badania histopatologicznego z analizą immunohistochemiczną. Leczenie przerzutów do przysadki mózgowej ma głównie charakter paliatywny i zależy od objawów klinicznych oraz od przebiegu choroby podstawowej. Obejmuje ono zastosowanie wazopresyny lub desmopresyny, leczenie systemowe, radioterapię, leczenie substytucyjne oraz postępowanie operacyjne. Rokowanie u chorych jest zwykle niekorzystne i przede wszystkim związane z agresywnością guza pierwotnego. Biorąc pod uwagę fakt, że najczęstszą kliniczną manifestacją zmian metastatycznych w przysadce jest moczówka prosta, w przypadku pojawienia się polidypsji i poliurii, koniecznie należy wykluczyć ich podłoże onkologiczne. Właściwe postępowanie może poprawić jakość życia chorych oraz pomóc w optymalizacji opieki nad pacjentami.

Słowa kluczowe: *przysadka mózgowa, moczówka prosta, przerzuty nowotworowe, optymalizacja opieki nad pacjentami*

Malignant neoplasms appear to be the most serious threat to the worldwide populations' health and life. Although the pituitary gland is not a common site for tumor metastases, lesions in this location have been observed with an increasing frequency during the last several decades. 2/3 of the pathologic masses are metastases of the lung and breast cancer. The aim of this review was to describe epidemiology, clinical manifestations (with diabetes insipidus as the most common symptom), management and prognosis of metastases to the pituitary gland (MPs). MPs are usually asymptomatic and occur in different stages of cancer or can even be its first symptom. The pituitary may be the only site of metastatic location. The posterior lobe is affected more frequently than the anterior lobe. If the symptoms are present, diabetes insipidus is the main presenting sign, sometimes being a first manifestation of cancer. Hyperprolactinemia or anterior pituitary insufficiency (masked by systemic complications of malignancy) occur less frequently. Clinical manifestations, MR images and history of cancer may be helpful to make a preliminary diagnosis but a final diagnosis can be made only after histopathological examination with immunohistochemical analysis. Treatment is mainly palliative and depends on the symptoms and the basic disease. It involves using vasopressin or desmopressin, systemic therapy, radiotherapy, replacement therapy and surgical procedures as well. The prognosis, which is usually unfavorable, depends on the course of the primary tumor. Considering the fact that the most frequent clinical manifestation is diabetes insipidus, in case of the polydipsia and polyuria occurrence it is necessary to exclude their oncological basis. Appropriate management may improve the quality of life and optimize patients' care.

Key words: *pituitary gland, diabetes insipidus, neoplasm metastases, optimizing patient care*

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Nadesłano: 11.02.2015
Zakwalifikowano do druku: 19.02.2015

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List of abbreviations

MPs – metastases to the pituitary gland
TPS – thickened pituitary stalk

Introduction

Endocrine syndromes can occur as a result of tumor metastases [1-6]. Metastases to the pituitary gland (MPs) have been reported in 0.14-28.1% of all brain metastatic lesions [7-10]. The first case of pituitary metastases was described in 1857 by L. Benjamin in a patient with melanoma [7, 8]. Although the pituitary gland is not a common site for metastatic lesions, masses in this location have been observed with an increasing frequency during the last several decades. This may be associated with the improvement in survival rates of patients with cancer as well as the development of more sensitive diagnostic techniques [6, 7, 11]. Some MPs are asymptomatic, while others are present with diabetes insipidus, which is the most common clinical manifestation of the disease [9, 12-16]. In both women and men, 2/3 of the pathologic lesions are metastases of the lung and breast cancer [6, 7]. The gastrointestinal tract and prostate cancers may also metastasize to the pituitary gland but with a lower frequency [7]. For instance, the incidence of liver tumors metastases (including *ca hepatocellulare*) is estimated at 1.1%. In approximately 3% of cases, despite intensive investigation, the primary neoplasm remains undetected [10, 17]. Prognosis, which is usually unfavorable, depends on the course of the primary tumor [6, 7].

The definition of diabetes insipidus

Diabetes insipidus is a group of symptoms characterized by hypotonic polyuria (>4l of urine per day, sp gr usually <1.005, osmolality <250 mOsm/kg) and polydipsia, caused by inadequate secretion of ADH (central diabetes insipidus) or an inadequate renal response to ADH (nephrogenic diabetes insipidus) [1,18-20]. Central diabetes insipidus is caused by congenital or acquired lesions, which damage the neurons in the supraoptic and paraventricular nuclei of the hypothalamus such as: tumors, malformations, injuries after surgery or trauma, haemorrhages, thromboses, infarctions and granulomatous diseases. The primary neoplasms, usually located in this area, are craniopharyngioma, meningioma and germinoma. Secondary tumors can also occur. 30-50% of the diabetes insipidus cases are related to an idiopathic disease [1,19-20].

Metastases to the pituitary gland may present with central diabetes insipidus [1, 21, 22].

Epidemiology and pathophysiology

Metastases to the hypothalamic-pituitary area are mostly asymptomatic and usually occur in patients with advanced cancers [2-6]. They are a part of generalized tumor spread and are associated with five or more metastatic locations, including those in bones. However, the pituitary gland may be the only site of metastatic location [16, 24-26]. Morita et al. [6] reported that in 56% of patients with MPs, metastases to the pituitary were the first manifestation of cancer. Some studies have shown that 13% of cases of intracranial metastases have not been connected with other distant sites of metastases [27]. MPs may be also incidental post-mortem findings [2-6]. In autopsy series, among 500 subjects with the history of cancer, pituitary metastases were found in 18 cases (3.6%). Six patients in this group suffered from breast cancer and only one person had clinical symptoms [2, 23]. On the other hand, some authors suggest that 20% of MPs are diagnosed clinically and diabetes insipidus is the main presenting symptom [3, 4, 27, 28]. Teers et al. [3] reported pathologic lesions in the pituitary gland (in the posterior lobe or in both anterior and posterior lobes) in 69.3% of 88 patients with malignancies; 6.8% of them had diabetes insipidus.

Breast cancer metastasizes to the pituitary gland with the highest frequency of all neoplasms. The incidence of breast cancer metastases to the hypothalamic-pituitary region ranges between 6% and 8%, and in autopsies this number can reach even 28% [27, 29-31]. It is thought that the PRL-rich pituitary gland is a particularly favorable environment for the proliferation of breast cancer cells [33, 34]. In patients suffering from leukemia or lymphoma, the frequency of MPs is reported at 2% to 46% [15, 32, 33].

The incidence of tumor metastases to the pituitary gland is presented in Table I.

Table I. Neoplasms metastasized to pituitary gland. Research conducted on 380 patients [7]

Tumor origin	Number of patients	% of patients
Breast	151	39.7
Lung	90	23.7
Gastrointestinal tract	24	6.3
Prostate	19	x5.0
Unknown origin	12	3.1
Kidney	10	2.6
Melanoma/skin cancer	9	2.4
Thyroid	8	2.1
Pancreas	5	1.3
Pharynx	5	1.3
Endometrium	5	1.3
Leukemia	5	1.3
Others	37	9.9

Pituitary metastases affect the posterior lobe more frequently than the anterior lobe [6, 13, 27]. It is suggested that the main reason for such location is the fact that the posterior lobe is supplied by the blood directly from the systemic circulation [13, 27, 35]. Furthermore, the closeness of dura simplifies the spreading of neoplasm from contiguous bones and the presence of metastases in bones increases the probability of pathologic lesions in the pituitary gland [27, 30, 36]. For instance, in a review of 178 cases of pituitary metastases, conducted by Max et al., the posterior lobe has been involved in 52% of patients, both lobes – in 27% and the anterior lobe only in 21% of subjects [13]. Similar results were observed in a study of 201 patients, where isolated neurohypophysis metastases and lesions coexisting with metastases to the adenohypophysis were found in 84.6% of subjects, whereas isolated metastases to the anterior lobe were detected in only 15.4% of cases [10].

Metastatic deposits in the anterior lobe are usually the result of neoplasm spreading from the posterior lobe [7, 40]. Anterior pituitary failure may be a consequence of vascular occlusion by cancer cells as well [3, 6, 13]. There is also a possibility of tumor invasion by leptomeninges and through the portal vessels [7, 36].

Clinical symptoms

The most common clinical presentation of metastases to the hypothalamic-pituitary region is diabetes insipidus, which occurs in even up to 71% of cases [29, 41]. Mc Cormic et al. [10] found diabetes insipidus in 70% of 40 patients with symptomatic pituitary metastases whereas only 15% of them had anterior pituitary failure symptoms. Hypopituitarism occurs less frequently than diabetes insipidus and if hypopituitarism is present it is usually accompanied by diabetes insipidus [9, 13, 42]. Secondary hypothyroidism and secondary hypoadrenalism are the most common manifestations of symptomatic anterior pituitary insufficiency. Systemic complications of malignancy and non-specific symptoms such as: fatigue, vomiting, weight loss and neurological disturbances may mask clinical symptoms of anterior pituitary failure [6, 7]. Therefore in patients with such symptoms, especially when they are not on chemotherapy, the possibility of tumor invasion of the pituitary should be kept in mind and appropriate diagnostic procedures should be performed [37].

Other symptoms including visual disturbances (bilateral hemianopsia) due to chiasmatic and optic nerve involvement, cranial nerves palsy, headaches and ophthalmoplegia are even more rare [13, 29, 43]. Tumor extension to the frontal lobes may result in cognitive deficit or psychiatric symptoms [2, 7, 29].

Hyperprolactinemia coexists with MPs in 6.3% of cases and is usually attributed to stalk compression [7]. It is very important to establish the degree of hyperprolactinemia to make a differential diagnosis of prolactinoma; PRL levels >200 ng/ml (9.0 nmol/l) indicate of PRL-secreting tumor whereas the highest PRL level reported in patients with MPs was about 150 ng/ml (7.0 nmol/l) [40].

The co-occurrence of posterior lobe insufficiency caused by the presence of MPs and primary adrenal insufficiency due to metastases to both adrenal glands occurs rarely [31, 47, 48]. Trincado et al. [48] reported the case of a patient with lung cancer (*a big-cell bronchogenic carcinoma*), whose first clinical symptom was diabetes insipidus caused by metastases to the hypothalamic-pituitary region; the patient had not only the posterior pituitary insufficiency but also the primary adrenal insufficiency due to bilateral metastases.

The incidence of clinical symptoms caused by metastases to the pituitary gland is presented in Table II.

Table II. Most common clinical symptoms of MPs. Study conducted on 190 subjects [7]. Some patients suffered from more than one symptom

Clinical symptoms	Number of patients	% of patients
Diabetes insipidus	86	45.2
Cranial nerve II deficit	53	27.9
Anterior pituitary insufficiency	45	23.6
Cranial nerve III, IV, VI	41	21.6
Headache	30	15.8
Fatigue/general malaise	15	7.9
Hyperprolactinemia	12	6.3
Pituitary apoplexy	9	4.7
Nausea/vomiting	7	3.7
Weight loss	6	3.1
Altered consciousness	5	2.6
Psychiatric deficit	5	2.6
SIADH	3	1.5
Cerebral hemorrhage	3	1.5
Cranial nerve V dysfunction	3	1.5
Other symptoms	13	6.5

Diagnosis

MRI is found to be the test of choice in the diagnosis of metastases to the pituitary gland [38, 49, 50]. A normal anterior pituitary lobe gives a strong signal which is most probably caused by a high amount of phospholipids and secretory granulations in the pituicytes [1, 28]. The loss of signal intensity in the nervous part of the pituitary on T1W1, the presence of metastases with high signal intensity on T2W1 and a thickened pituitary stalk may indicate tumor infiltration [29, 50, 52]. Moreover, the manifestation of an isodense or hypodense mass on T1W1 images is suspected to be a metastatic lesion [7]. These

metastases may have the form of tumors or cysts [37, 38]. However, none of the pathologies described above are exclusively specific for cancer metastases [44, 46, 52].

The most common CT / MR characteristics for metastases to the pituitary gland are presented in Figure 1.

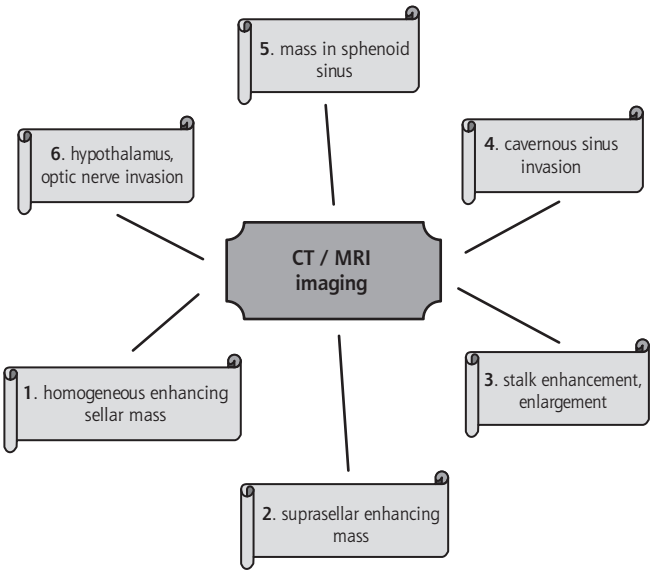

Fig. 1. CT/MR characteristics for pituitary metastases, based on Morita, et al. [6]. Numbers from 1 to 6 indicate prevalence of type of pathologic lesion where 1 – is "the most common" lesion and 6 – is "the rarest" lesion

Differential diagnosis

During examination of the pituitary, the presence of benign lesions as well as malignant tumors should be considered [6, 7]. It is well known that metastases to the pituitary gland may imitate adenomas [11, 25, 44] and other benign or malignant lesions of the sella turcica including granulomas, cysts, aneurisms, injuries, infarctions, abscesses and craniopharyngiomas, which makes the diagnosis more difficult, particularly when cancer has not been detected before [46, 54-57]. In autopsy series of 500 patients with a history of cancer, MPs have been found in 3.6% of cases and pituitary adenomas in 1.8% of patients [13]. It is not easy to perform a differential diagnosis of MPs and adenomas [2, 13, 44]. However, there are certain features which may strongly indicate the presence of pituitary metastases [13, 35, 44]. Firstly, adenomas and metastases in the hypothalamic-pituitary region manifest with different clinical symptoms and neuroradiological features [27, 30, 58]. For instance, diabetes insipidus occurs in less than 2% of patients with adenomas [7, 51, 59]. Thus, Schubiger and Haller [60] suggest that it is the most important criterion which distinguishes metastases from adenomas. Moreover, if cranial nerve palsy occurs, there is an increased likelihood that metastases are present [7, 26]. On the other hand, hypopituitarism, headaches and visual disturbances are less helpful in a differential diagnosis [6, 44, 60]. Secondly, images of the anterior lobe such as a thickened pituitary stalk (TPS) and infiltration of the cavernous sinus observed in the MRI may indicate the presence of metastases in the pituitary [29]. However, other causes of TPS i.e. histiocytosis, granulomatous diseases, germ cell tumor and lymphoma should be excluded. Isolated metastases to the pituitary stalk account for 2% of all metastases to this gland [3, 44, 61].

Thus, a fast-growing tumor in the hypothalamic-pituitary region which is aggressively infiltrating the surrounding tissue [24, 45, 60], especially in patients treated with dopamine agonists [7, 25, 44], or a sudden occurrence of the symptoms of diabetes insipidus, ophthalmoplegia and severe headaches in a patient with a history of cancer [10, 24, 44], may be likely indications of MPs [45, 62, 63]. However, only a histopathological examination with immunohistochemical analysis can confirm this diagnosis [2, 27, 64]. Specimens for the analysis are taken during diagnostic procedures, namely microcraniotomy or transphenoidal biopsy [61].

Stage of disease and diabetes insipidus

Diabetes insipidus may occur in the course of cancer, which has been already diagnosed, or be its first manifestation [59, 64, 65]. In a group of 190 patients with symptoms suggesting the presence of metastases in the pituitary gland, the primary tumor was found during detailed tests in 43.7% of patients. In over 7% of cases the pituitary gland was the only site of the metastases [44, 45, 60]. Similar results were obtained in a study involving 20 patients with clinical symptoms indicating metastases to the hypothalamic-pituitary region. In as many as 56% of the patients MPs were the first manifestation of an ongoing disease process [6]. On the other hand, Netelenbos et al. [1] described the case of a 57-year-old patient with a recurrence of cancer after a five-year period of remission, who had diabetes insipidus associated with partial posterior pituitary lobe insufficiency and primary adrenal insufficiency (bilateral metastases) in the course of a systemic spread of cancer. In turn, Dogan et al. [37] reported an even longer case of cancer remission (17 years), in a 62-year-old patient with a recurrence of breast cancer, metastases to the pituitary stalk and symptoms of diabetes insipidus. A similarly long period of remission was observed by Bobilev et al. [27].

Treatment

Treatment of metastases to the pituitary gland is mainly palliative and depends on the clinical symptoms as well as the systemic spread of metastases [10, 11, 24].

Patients diagnosed with diabetes insipidus, including those with MPs, respond well to treatment with vasopressin and its synthetic analogue, desmopressin [21, 22]. Although many studies show that administering desmopressin to such patients does not prolong their lives and is used exclusively to treat the symptoms, it does increase their quality of life [2, 7, 37].

As far as curing the patient is concerned, the most reasonable solution seems to be a combination of systemic treatment with local radiotherapy [2, 7]. Radiotherapy can be also a treatment of choice if diabetes insipidus or oculomotor nerve palsy are present. Furthermore, it is a method of choice in the case of a generalized, systemic spread of cancer [13, 16, 35].

Non-invasive stereotactic radiosurgery is another option. This form of radiotherapy, which is also known as a gamma knife, consists in focusing beams emitted from cobalt-60 on the cancerous lesions, leading to the destruction of cancer cells but simultaneously protecting the remaining tissue. Prior use of traditional radiotherapy does not preclude a later use of this method [37, 39].

Surgical procedures are only performed in patients with suprasellar expansion of metastases, associated with a deterioration of vision or very severe headaches [11, 24, 44]. However, in the case of disseminated cancer complete resection is not possible [7, 27, 30]. It is known that surgical treatment does not prolong the lives of such patients significantly, but it has a positive impact on their quality of life [6, 29, 66,].

In panhypopituitarism or partial insufficiency of the posterior pituitary lobe, the replacement therapy is used [1, 7, 61].

Prognosis

The prognosis for patients with metastases to the hypothalamic-pituitary area is unfavorable, mainly due to the aggressiveness of the primary tumor and to a lesser extent to the location of the metastases [7, 68].

A complete remission of the symptoms of diabetes insipidus is possible only when effective anti-cancer treatment is applied [4]. Since there is no barrier between the blood and brain in the pituitary stalk region, thanks to combining advanced local radiotherapy and systemic treatment, including chemotherapy, hormone therapy with the use of letrozole and targeted therapy with the use of trastuzumab in HER2-positive breast cancer, a satisfactory result can be achieved [27, 61, 69]. Out of 19 patients with metastases to the hypothalamic-pituitary region observed by Kimmel et al. [5], diabetes insipidus subsided in only one of them as a result of radiotherapy. Yap et al. [4] noticed a remission of symptoms in 4 out of 39 patients with breast cancer after chemotherapy associated with hormone therapy [2]. Diabetes insipidus rarely subsides on its own or appears, disappears and recurs as a result of nerve fiber regeneration [7, 45].

The survival rate for patients with diagnosed MPs ranges from 6 to 22 months [29, 37, 70]. Patients with isolated metastases to the hypothalamic-pituitary region tend to live longer [7, 9, 27]. The described longest survival time was 5 years [6]. The unfavorable prognosis is mainly due to the aggressive development of the primary disease [7, 68]. Most patients die within a few months after diabetes insipidus has been diagnosed [2, 6, 37]. Ntyonga-Ponto et al. [46] emphasize the fact that only about 10% of patients live longer than a year since the disease diagnosis.

The pituitary metastases in a general perspective of public health

Nowadays, malignant tumors appear to be not only the chronic diseases but also the most serious threat to the worldwide populations' health and life. What is more, there is a clear evidence that cancer will continue to represent an important challenge both to local health authorities and the National Health Fund [71, 72]. For many years malignant neoplasms have remained the second leading cause of death, accounting for about 25% of all deaths. In the near future, the prevalence of cancer is projected to rise in women as well as in men and is expected to be the common health problem among people of working age [71, 73]. It has been reported that in Poland in 2008, the prevailing tumors in men were: lung cancer, prostate cancer, colon cancer and stomach cancer (21.6%, 12.6%, 12.2% and 5.0% respectively) while breast cancer, colon cancer, lung cancer and reproductive organs tumors - uterine cancer, cervical cancer and ovary cancer were the most commonly registered neoplasms in women (22.2%, 10.1%, 8.1% and 7.3%, 5.0%, 5.0% respectively) [71].

It should be noted that the most prevalent cancers are simultaneously the most common malignant neoplasms metastasized to the pituitary gland because data indicate that in both women and men the metastases of lung cancer and breast cancer account for about 2/3 of the metastatic lesions to the pituitary. Less frequently metastases are connected to the presence of the gastrointestinal tract or prostate cancers [6, 7]. Taking into consideration the increasing prevalence of malignant tumors, it is expected that the incidence of MPs as well as of the MPs-associated symptoms will rise consequently.

As the prevalence of malignant neoplasms increases, there is a need for permanent training and raising the awareness of health care workers on possible symptoms and management of subjects with metastases, including MPs.

Conclusion

Metastases to the hypothalamic-pituitary region can occur in different stages of cancer or even be its first symptom. Considering the fact that the most frequent clinical manifestation of MPs is diabetes insipidus, in case of the polydipsia and polyuria occurrence it is necessary to exclude their oncological basis while trying to establish their origin.

Adequate knowledge, concerning not only the well-known diseases but also less frequent health problems such as MPs and their symptoms, is needed to optimize patients' management. Even though the proper diagnosis does not prolong survival rate, the use of appropriate therapy and relevant cancer care can definitely improve the quality of life in patients with malignant neoplasms, including MPs. Furthermore, it may help to prevent complaints against doctors and health care institutions regarding misdiagnosis, delayed diagnosis or omission of proper therapy.

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