



Spontaneous regression of non-functioning pituitary adenoma due to pituitary apoplexy following anticoagulation treatment — a case report and review of the literature

Udar nieczynnego hormonalnie gruczolaka przysadki w trakcie leczenia przeciwzakrzepowego z następową jego samoistną regresją — opis przypadku i przegląd piśmiennictwa

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Abstract

Pituitary apoplexy (PA) is a rare, potentially life-threatening medical condition due to acute ischaemia or haemorrhage of the pituitary gland. The main clinical features are: abrupt onset of severe headache, nausea, vomiting, deteriorating level of consciousness, visual impairment and/or endocrine deficiency. Correct and prompt diagnosis is essential for effective therapy, but there are no randomised studies or strict recommendations defining treatment modalities. We present the case of a 59 year-old woman with pituitary tumour apoplexy, presenting with severe headache, vomiting and visual field deterioration. The patient was treated conservatively because of her refusal of surgery and was followed-up for five years. In the course of treatment, recovery of the visual field defects, as well as right sixth cranial nerve paresis, was observed. Repeated magnetic resonance imaging (MRI) revealed regression of the tumour without signs of its re-growth. We discuss therapeutic modalities with particular emphasis on morbidity and review the literature relating to the management of pituitary tumour apoplexy. (*Endokrynol Pol* 2013; 64 (1): 54–58)

Key words: pituitary apoplexy, hypopituitarism, deep venous thrombosis, pituitary tumour, transphenoidal surgery

Streszczenie

Udar przysadki jest rzadkim, potencjalnie zagrażającym życiu stanem spowodowanym martwicą niedokrwienną lub krwotoczną. Główne objawy kliniczne udaru przysadki to nagły, silny ból głowy, nudności, wymioty z towarzyszącym pogorszeniem stanu świadomości, zaburzeniami widzenia i upośledzeniem czynności hormonalnej przysadki. Prawidłowe i szybkie rozpoznanie tego stanu ma podstawowe znaczenie dla wdrożenia właściwego leczenia. Dotychczas nie przeprowadzono badań randomizowanych oraz nie opracowano zaleceń wpływających na poprawę skuteczności leczenia udaru przysadki. Autorzy pracy opisują przypadek 59-letniej kobiety hospitalizowanej z powodu silnego bólu głowy, wymiotów i zaburzeń widzenia w przebiegu udaru przysadki. Chora nie wyrażała zgody na leczenie operacyjne i była leczona zachowawczo, a następnie poddana pięcioletniej obserwacji ambulatoryjnej. W trakcie hospitalizacji obserwowano poprawę pola widzenia oraz powrót prawidłowej czynności nerwu odwodzącego prawego. Kontrolne badanie MR przysadki wykazało regresję gruczolaka bez cech jego wznowy w czasie pięcioletniej obserwacji. Autorzy analizują różne metody leczenia udaru przysadki z uwzględnieniem ich następstw (powikłań) oraz prezentują na podstawie przeglądu piśmiennictwa wskazania terapeutyczne. (*Endokrynol Pol* 2013; 64 (1): 54–58)

Słowa kluczowe: udar przysadki, niedoczynność przysadki, żylna choroba zakrzepowo-zatorowa, guz przysadki, operacja przezklinowa

Introduction

Pituitary apoplexy (PA) is a rare, potentially life-threatening medical condition caused by acute ischaemia or haemorrhage in the pituitary gland [1]. Percival Bailey first reported a massive, fatal haemorrhage to the pituitary tumour in 1898 [2]. Another case of a fatal haemorrhage in a somatotroph pituitary adenoma was described by Bleibtreu in 1905 [3]. In 1950, Brougham et al. presented the first comprehensive study of five patients and coined

the term 'pituitary apoplexy' [1]. Over the past 30 years, several case reports and small series have emphasised the association of different predisposing factors with PA.

The main clinical features of PA are: abrupt onset of severe headache, nausea, vomiting, deteriorating level of consciousness, visual impairment and/or endocrine deficiency. Correct and prompt diagnosis is essential for effective therapy but there are no randomised studies or national recommendations defining treatment modalities.



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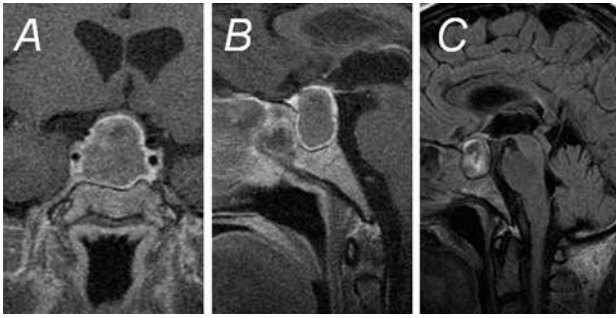


Figure 1. Gadolinium-enhanced T1-weighted sagittal and coronal MRI (A, B) and FLAIR sagittal (C) of the pituitary gland showing a $27 \times 24 \times 15$ mm mass indicative of infarctive pituitary apoplexy with extension toward the right cavernous sinus and upward displacement of the optic chiasm. Enlargement of the sella turcica with typical thickening of the sphenoid sinus mucosa is visible

Rycina 1. Badanie MR, po podaniu środka kontrastowego w czasie T1-zależnym, w przekroju strzałkowym i czołowym (A, B) oraz przekroju strzałkowym w sekwencji FLAIR (C) uwidoczniło gruczolak przysadki o wymiarach $27 \times 24 \times 15$ mm. Guz nacieka prawą zatokę jamistą i uciska skrzyżowanie wzrokowe. Widoczne cechy udaru niedokrwiennego guza z towarzyszącym powiększeniem siodła tureckiego i charakterystycznym dla udaru pogrubieniem błony śluzowej zatoki klinowej

Case report

A 59 year-old, postmenopausal woman was admitted to the hospital following an episode of severe headache, nausea, vomiting and dizziness of around two weeks' duration prior to admission. Additionally, the patient had experienced progressive visual impairment for the past six days. Six weeks prior to hospitalisation, deep vein thrombosis of the left lower extremity was diagnosed and a graded compression stocking and low molecular weight heparin (LMWH — Fraxiparine 60 mg s.c. daily) was initiated. The patient was obese but without clinical symptoms of Cushing's disease or acromegaly. The neurological and ophthalmological examination performed after admission to the Department of Neurosurgery revealed a decrease of visual acuity to 0.5 in both eyes, bilateral temporal field restriction, and diplopia. There was a limitation of abduction on the right side. The optic discs were normal in colour and shape. Apart from the visual impairment, neurological examination was normal. There were no signs of focal deficits, especially in terms of remaining cranial nerves. Vital signs and intracranial pressure was also normal. On the basis of full blood count and coagulation tests, clotting disturbances and heparin-induced thrombocytopenia (HIT) were excluded. Only the serum sodium level was slightly elevated to 148 mmol/L. Magnetic resonance imaging (MRI) revealed a pituitary tumour apoplexy (Fig. 1A, B, C).

In order to assess the pituitary function, hormone measurements were performed and their results confirmed secondary adrenal insufficiency (Table I). The remaining hormone concentrations were within normal limits. There were no clinical signs of diabetes insipidus. Based on obtained results, pituitary tumour apoplexy with signs of secondary adrenal insufficiency was diagnosed. Treatment with hydrocortisone was initiated at a dose of 200 mg i.v (t.i.d.), intravenous fluid replacement therapy and analgesia. The patient was treated conservatively because of lack of consent for surgical intervention. In the course of this treatment, the patient's neurological state gradually and uneventfully improved. The visual abnormalities and right sixth cranial nerve paresis completely resolved. The patient was finally discharged on the 16th day of hospital stay on hydrocortisone replacement therapy (at a dose of 30 mg/24 h).

The next hormone assessment performed three months later revealed multihormonal insufficiency of the anterior pituitary. Levothyroxine supplementation at a dose of 50 μ g/24 h was initiated, and hydrocortisone replacement therapy was continued. MRI of the pituitary performed three months later revealed no residual pituitary adenoma and a picture of secondary empty sella with slight displacement of the optic chiasm into the sella (Fig. 2A and B). The patient has been constantly followed-up in our outpatient clinic. In MRI repeated five years after the incidence of PA, there were no signs of tumour re-growth (Fig. 2 C and D). A complete insufficiency of the anterior lobe of the pituitary was confirmed, and continuous replacement therapy with hydrocortisone and levothyroxine was recommended at a dose of 30 mg/24 h and 100 μ g, respectively.

Discussion

A correct diagnosis of PA can prove challenging. Mortality and morbidity are predominantly caused by the delay in diagnosis and the lack of decision as to adequate therapy. The incidence of pituitary apoplexy is highly variable. Intratumoural haemorrhage and/or ischaemic infarction are not necessarily associated with clinical apoplectic events. Sometimes they might be a form of degeneration of the neoplasm [4]. Its incidence is estimated at 9–15%. PA has been reported to occur with a frequency ranging from 0.6 to 30% [1]. It can occur at any age, with its peak in the fifth decade. Neither sex predominates.

The exact pathogenesis of PA is not completely understood. Biousse et al. identified four groups of so-called precipitating conditions considered as triggering factors for PA [5]: 1) The reduced blood flow within the pituitary or the tumour, caused either by hypotension or transient increase of intracranial pressure; 2) An acute

Table I. Hormonal test values measured on admission and after three months**Tabela I. Wyniki badań hormonalnych wykonane przy przyjęciu do szpitala oraz po 3 miesiącach od przebytego udaru guza przysadki**

	Measured value		Reference range
	On admission	After three months	
GH	0.18 µg/L	0.13 µg/L	< 5 µg/L
IGF-I	128 µg/L	69 µg/L	180–325 µg/L
ACTH	–	13.2 pg/mL	10–60 pg/mL
Cortisol	< 1 µg/dL	< 1 µg/dL	7–25 µg/dL
TSH	1.31 mIU/mL	0.19 mIU/mL	0.3–3.5 mIU/mL
FT4	0.89 ng/dL	0.52 ng/dL	0.8–2.0 ng/dL
LH	9.62 mIU/mL	0.41 mIU/mL	10.4–64.6 mIU/mL
FSH	49.7 mIU/mL	0.59 mIU/mL	26.7–133.4 mIU/mL
PRL	13.1 ng/mL	18.6 ng/mL	< 20 ng/mL
Oestradiol	< 20 pg/mL	< 20 pg/mL	0–30 pg/mL

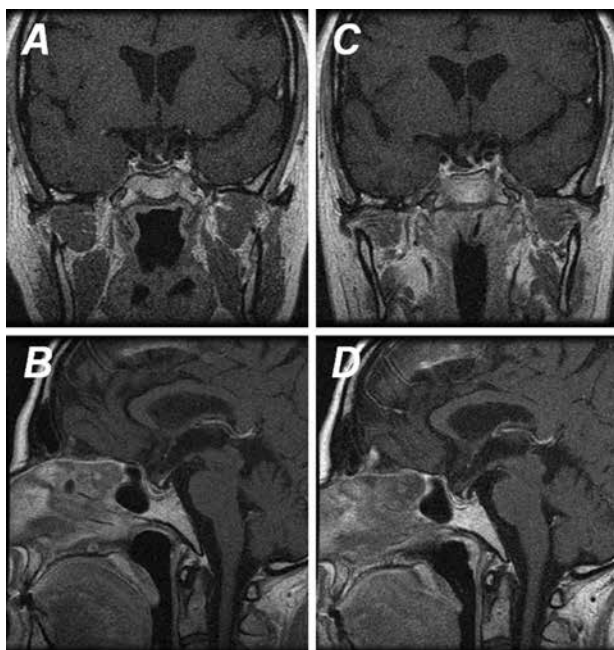


Figure 2. Gadolinium-enhanced T1-weighted sagittal and coronal MRI three months (A, B) and 60 months (C, D) after the apoplectic event showed complete resolution of the pituitary tumour. Secondary empty sella with left, lateral displacement of the pituitary stalk and flattened pituitary gland are seen. Optic chiasm is distorted and drawn to the sella

Rycina 2. Badanie MR po podaniu środka kontrastowego w czasie T1-zależnym, w przekroju czołowym i strzałkowym po trzech miesiącach (A, B) oraz po 60 miesiącach (C, D) od epizodu udaru przysadki wykazało regresję gruczolaka. Widoczne wtórnie puste siodło tureckie z przemieszczeniem szypuły przysadki na stronę lewą. Skrzyżowanie wzrokowe jest przemieszczone i pociągane do siodła tureckiego

increase in blood flow within the pituitary tumour; 3) A hyperstimulation of the pituitary by oestrogen or due to dynamic testing (TRH, GnRH); and 4) Factors predisposing to anticoagulation (such as: haematologic diseases, anticoagulant therapy, thrombolytic agents). It is commonly accepted that prompt and correct diagnosis of PA is essential in terms of further treatment and patient prognosis. The differential diagnosis includes: subarachnoid haemorrhage, aneurysmal rupture, infectious meningitis, temporal arteritis, migraine, intracerebral spontaneous haemorrhage, optic neuritis and cavernous sinus thrombosis [1].

LMWH is a widely accepted treatment of deep venous thrombosis [6]. However, such a treatment might lead to HIT which is the most feared complication of LMWH. It is characterised by a decrease in platelet count by 50% or to a number less than 100,000/mm³ occurring usually between the fifth and the 14th day of therapy [7].

In the presented case, standard anticoagulant therapy triggered a haemorrhage within a previously undiagnosed pituitary tumour. On the basis of complete blood count, HIT was excluded. Simultaneously, administration of LMWH was continued because of the coexistence of serious risk factors of thromboembolic events (active deep venous thrombosis, prolonged immobilisation, indwelling central venous catheter and prolonged hydrocortisone treatment).

Currently, MRI is considered to be more effective than computed tomography (CT) in detecting pituitary lesions and is the imaging method of choice for identifying the features of PA [1, 8]. On MRI, PA may present as

either an infarction or haemorrhage. In a case of infarctive PA, no intrasellar haemorrhage is seen in MRI. The tumour mass has low signal intensity on T1-weighted and T2-weighted MRI and no enhancement is seen after gadolinium administration, with the exception of peripheral enhancement of the tumour's capsule in acute, subacute and chronic phases of this condition [9]. Peripheral enhancement is not typical for infarctive PA and can also be seen in cases of cystic pituitary adenomas and craniopharyngiomas [8]. In the presented case, pathological sellar mass had a dark signal in T1-weighted images and rim enhancement was observed, but T2-weighted images suggested intratumoural haemorrhage. Furthermore, a massive thickening of the sphenoid sinus mucosa was present. This phenomenon was first described by Arita et al. [10]. They speculated that thickening of the sphenoid sinus mucosa is caused by venous congestion due to a sudden increase of intrasellar pressure. Liu and Couldwell reported that the presence of sphenoid sinus mucosa thickening following PA might be accompanied by an increased rate of cranial nerves deficits at presentation [3]. This finding appears to be associated with worse endocrinological (hypopituitarism and subsequent long-term hormonal replacement therapy) and ophthalmological outcomes. [9]. In the reported case, it also seems that visual impairment at presentation and post-apoplectic pituitary insufficiency might be related to the thickening of the sphenoid sinus mucosa detected in MRI.

The spontaneous regression of hormone secreting pituitary adenomas following PA is a well known phenomenon [11–14]. Quoted authors have reported "spontaneous recovery" from hormone hypersecretion and concomitant endocrine symptomatology. According to Kamiya et al., late recurrences of the primary endocrinopathy and tumour regrowth following PA is often observed [15].

In cases of non-functioning pituitary tumours (which are ordinarily macroadenomas), a spontaneous disappearance caused by PA is rarely seen [16, 17]. Early adenoma regrowth is often noted, and surgery is the recommended treatment modality because tumour growth is usually accompanied by 'mass effect' and visual field abnormalities [18]. Furthermore, if PA results in a secondary empty sella, displacement of the optic chiasm into the sella might complicate visual outcome [17].

Besides, non-functioning pituitary adenomas treated surgically recur more commonly in patients with residual tumour [2]. Chen et al. reported a higher rate of tumour regrowth in a series of non-functioning pituitary adenomas following pituitary tumour apoplexy

compared to non-apoplectic tumours [19]. For now, there is no rational explanation for this phenomenon.

In our centre, an immediate surgical intervention in a case of haemorrhagic pituitary tumour apoplexy is usually recommended. In the reported case of a non-functioning pituitary adenoma, both a clinical presentation and MRI results were strongly suggestive for infarctive PA. Additionally, the patient refused to undergo pituitary surgery. Thus we had the opportunity to observe a natural history of the pituitary tumour apoplexy treated conservatively. Its complete disappearance was documented in serial MR images over the course of five years of follow-up. In our opinion, clinically evident pituitary infarction destroyed the whole tumour, in contrast to cases of intratumoural haemorrhage, in which only part of the tumour is usually damaged.

It cannot be determined whether conservative or more invasive management provides better results in such difficult cases. Most authors recommend prompt neurosurgical intervention in patients with symptoms such as: diminished level of consciousness, prominent visual disturbances and neurological deficits [20,21]. They argue that immediate debulking surgery leads to better neurological and endocrinological outcomes. However, in some studies, medical therapy is advocated [22]. Ayuk et al. and Sibal et al. reported no significant differences in terms of recovery of the pituitary function and visual impairment between patients treated conservatively and surgically [22, 23]. Gruber et al. found no evidence that a surgical approach is characterised by a better outcome [24]. A review of the literature by Nishioka et al. showed that pituitary insufficiency usually develops following haemorrhagic apoplexy, whereas pituitary function is more commonly preserved after infarctive apoplexy [12].

Considering the above, hormone replacement following PA is indispensable for nearly 80% of patients. There have been no significant differences confirmed between surgically and conservatively treated patients [9]. With regards to visual outcomes, better results are more likely in patients after prompt neurosurgical intervention [25]. In the presented case, a conservative treatment provided excellent neuro-ophthalmologic results, but permanent pituitary insufficiency occurred.

In such a life-threatening case, the appropriate treatment is crucial for mortality, morbidity and further prognosis. The most important issue is to emergently stabilise the patient's general condition. Pituitary function is usually violently compromised. Therefore (following endocrine evaluation), the rapid intravenous administration of high dose glucocorticosteroids is recommended [1, 9, 22, 23].

It should be stated that the incidence of tumour recurrence after pituitary tumour apoplexy is not known. Randeve et al. observed adenoma regrowth in 6% of patients following PA surgery [20]. Gruber et al. reported later relapse of a pituitary adenoma after an apoplectic event in 23% of patients [24]. Therefore, all patients after PA require prolonged endocrine and imaging follow-up as well as close collaboration between neurosurgical and endocrinological teams. In terms of frequency of imaging studies, Rajasekaran et al. recommended the implementation of MRI 3-6 months after an episode of PA, then once per year for five years and every two years thereafter [9].

Conclusion

In the described case, the tumour infarction (infarctive PA) destroyed the whole clinically evident pituitary tumour, unlike an intratumoural haemorrhage (haemorrhagic PA) when only part of the tumour is usually damaged. We think that, in selected cases, pituitary tumour apoplexy could be treated conservatively. Such a treatment may result in resolution of neurological disturbances, although the pituitary insufficiency might be permanent. Additionally, the presented case confirms that PA may be the first manifestation of pituitary adenoma and highlights an increasing problem in patients on anticoagulant therapy.

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