



## Postpartum hypothalamic dysfunction — a case report

Poporodowe zaburzenia czynności podwzgórza — opis przypadku

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### Abstract

Hypothalamic dysfunction is a rarely diagnosed endocrine disorder resulting from various pathological processes affecting this brain region. It is characterized by a complex clinical manifestation, including headaches, abnormal regulation of various behaviours, abnormalities in sleeping and thermoregulation, and inappropriate secretion of many hormones. In our paper, we report the case of a 29-year-old female in whom hypothalamic dysfunction was induced by delivery complications. Accurate diagnosis of this syndrome required complex laboratory and imaging tests. The disease-related obesity was resistant to conventional treatment (diet and pharmacotherapy) and only bariatric surgery caused a reduction of body mass. The described patient is the first with postpartum hypothalamic dysfunction in whom plasma levels of adipokines, neuropeptides, and alimentary tract hormones contributing to physiological regulation of food intake were assessed. (*Pol J Endocrinol* 2010; 61 (4): 396–399)

**Key words:** postpartum hypothalamic dysfunction, clinical picture, obesity, pathogenesis, treatment

### Streszczenie

Zaburzenia czynności podwzgórza stanowią rzadko rozpoznawaną jednostkę kliniczną, stanowiącą konsekwencję różnych procesów patologicznych toczących się w obrębie tej struktury mózgu. Charakteryzuje ją złożony obraz kliniczny, na który składają się bóle głowy, nieprawidłowa regulacja łaknienia i pragnienia, zaburzenia snu i termoregulacji oraz nieprawidłowe wydzielanie hormonów. W niniejszym artykule opisano przypadek 29-letniej kobiety, u której doszło do rozwoju zaburzeń czynności podwzgórza w następstwie powikłań okołoporodowych. Postawienie prawidłowego rozpoznania wymagało wykonania wielu oznaczeń laboratoryjnych i przeprowadzenia badań obrazowych. Otyłość, która wystąpiła u pacjentki, wykazywała oporność na klasyczne leczenie (dietyczne i farmakologiczne) i dopiero leczenie bariatryczne spowodowało redukcję masy ciała. Opisywana pacjentka jest pierwszą chorą z poporodową dysfunkcją podwzgórza, u której wykonano oznaczenia stężeń w osoczu adipokin, neuropeptydów i hormonów przewodu pokarmowego uczestniczących w fizjologicznej regulacji poboru pokarmu. (*Endokrynol Pol* 2010; 61 (4): 396–399)

**Słowa kluczowe:** poporodowe zaburzenia czynności podwzgórza, obraz kliniczny, otyłość, patogeneza, leczenie

### Introduction

Hypothalamic dysfunction, formerly known as hypothalamosis or diencephalosis, is a rarely diagnosed endocrine disorder which is a consequence of abnormal activity of the hypothalamus [1, 2]. The hypothalamus is one of the most crucial regions of the brain, which controls hunger, thirst, body temperature, and circadian cycles and is considered a link between the nervous and endocrine systems [3–5]. Although hypothalamic dysfunction may result from various pathological processes within the central nervous system, most cases of this disorder described to date concern young women

who underwent a difficult delivery or abortion, and for these cases some authors use the Latin term *hypothalamosis post graviditate*. Other disorders leading to the development of diencephalosis are: traumas, intoxications, or infections [1, 6]. The clinical manifestation of hypothalamic dysfunction differs markedly between patients. However, the most frequently reported symptoms include obesity, abnormal feeding behaviour (anorexia or excessive eating), a disturbed regulation of thirst (polydipsia or adipsia), vegetative dysfunctions (headaches, cramping abdominal pains, and diaphoresis), sleeping disturbances (narcolepsy, insomnia, periodic attacks of sleep), abnormal thermoregulation



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(hypo- or hyperthermia), disturbances in the psychic sphere (neurasthenia, depression), and abnormal secretion of various hormones, especially vasopressin or oxytocin deficiency, hypogonadism, or hyperprolactinaemia [2].

In recent years, hypothalamic dysfunction has been diagnosed very rarely, which may be explained by a better understanding of the pathophysiological processes within the hypothalamus and its surrounding structures, an improvement in brain imaging procedures, and better care of females during the periparturient period. In some cases, the cause of a rare diagnosis may also be the unclear definition and lack of uniform diagnostic criteria of this disorder. For these reasons, some authors even reject the existence of this clinical entity, which, in our opinion, is not the case. In the present study, we reported a 29-year-old woman with delivery-induced hypothalamic dysfunction. Apart from the description of the patient's clinical picture, our study is the first which has determined plasma levels of adipokines, neuropeptides, and alimentary tract hormones contributing to a physiological regulation of food intake and body mass in any individual suffering from this syndrome. Their measurements enabled us to verify the hypothesis that hypothalamic dysfunction is associated with a disturbed function of adipose tissue or with abnormal activity of the gut-brain axis.

### Patient's presentation

A 29-year-old woman was admitted to our clinic in order to determine the cause of a dramatic increase in body mass. Before first pregnancy in 2005 her body mass was 55 kg and her body mass index (BMI) was 19.5 kg/m<sup>2</sup>. During the first pregnancy she felt well and no complications were noticed until delivery. Labour was complicated by the incorrect position of the foetus. For this reason and because of insufficient progress of the labour, the gynaecologists decided to perform a caesarean section. As a result of this operation and increased haemorrhage in the third stage of labour, the patient lost about two litres of blood and blood pressure decreased to 80/60 mm Hg. Consequently, the patient had to be given erythrocyte mass and fresh frozen plasma transfusions together with crystalloids and colloids to restore the appropriate volume of the vascular bed. Although during the first pregnancy her weight gain was 12 kg, after the labour it decreased only by 8 kg, and almost at once started to rise. During the following 11 months preceding the patient's second pregnancy, her body mass increased from 59 to 69 kg, and BMI from 20.9 to 24.4 kg/m<sup>2</sup>. The weight gain was accompanied by headaches and abdominal pains of different localization and intensity, dizziness, heart palpitations, trem-

or, excessive sweating, alternate periods of oligodipsia and polydipsia, and abnormalities in menstrual cycle, which were absent before the first gestation. Eleven months after her first gestation, the patient became pregnant for the second time. Although the above-mentioned symptoms did not disappear, their intensity remained at a similar level throughout the pregnancy. Gestation, during which weight gain reached 5 kg, ended in the second caesarean section performed because of obstetric indications. After delivery, the patient's body mass, which returned to the pregestational value, started dramatically increasing (20 kg within six months). The above-described symptoms became much more pronounced than in the period between both pregnancies. Moreover, the patient started to experience new symptoms, such as alternative periods of binge eating and fasting, paroxysmal insomnia, attacks of flushing of the face and neck, and almost complete loss of libido. Lactation was undisturbed and therefore she breastfed her child for four months. After lactation, her menses became sparse and irregular, and therefore oral contraceptive pills, containing ethinyl estradiol (35 µg) and norgestimate (250 µg) were prescribed. An unacceptable increase in body mass led to depressive symptoms and to several-week periods of dramatic reduction in food consumption and very intense exercise. Despite diet restrictions and regular physical activity, the body mass did not change, and therefore the patient was prescribed (by a general practitioner) sibutramine. Two months later, due to lack of effect, sibutramine was replaced with orlistat, which also did not result in a reduction in body mass. The significant weight gain of 20 kg since the second labour (BMI increased to 31.5 kg/m<sup>2</sup>), with no significant effect of both non-pharmacological and pharmacological treatment, and the range of accompanying complaints meant that the patient was admitted to our clinic.

On admission, apart from the increased waist circumference (114 cm), the patient did not have other abnormal characteristic for metabolic syndrome (blood pressure — 125/80, triglycerides — 134 mg/dL, HDL cholesterol — 52 mg/dL, plasma fasting glucose — 85 mg/dL). Two-hour post-challenge plasma glucose, plasma insulin, and homeostatic model assessment (HOMA) ratio were, respectively, 132 mg/dL, 10.5 mIU/L, and 2.2. During hospitalization, we performed complex diagnostics including both hormonal and imaging tests. We excluded hypothyroidism (TSH — 0.791 mU/L, fT<sub>4</sub> — 0.96 ng/dL, fT<sub>3</sub> — 3.66 pg/mL), Cushing syndrome (cortisol suppression after 1 mg of dexamethasone to 0.99 µg/dL; urine free cortisol — 68 and 62 µg/day, reference values: 20–90; plasma DHEA-S — 242.6 µg/dL, reference values: 80–450), polycystic ovary syndrome (normal levels of testosterone, androstendione, normal free androgen index, lack of clinical manifestations of androgen excess and of typi-

cal ultrasonographic features in the ovaries), congenital adrenal hyperplasia (17-hydroxy-progesterone at baseline — 0.34 ng/mL, and after Synacthen administration — 1.14 ng/mL), insulinoma (fasting insulin — 10.2 mIU/L, reference range: 5–25; fasting C-peptide — 2.65 ng/mL, reference range: 0.55–2.9; the normal result of the fasting test), GH deficiency (IGF-I levels within the reference range — 137 ng/mL; the normal response of GH to insulin-induced hypoglycaemia (an increase from 1.7 to 11.2  $\mu$ g/L) and pseudohypoparathyroidism (negative history, normal PTH levels). We also excluded pituitary disorders induced by pregnancy or labour (Sheehan's syndrome and hypophysitis). Plasma osmolarity (287 mOsm/kg H<sub>2</sub>O) and plasma sodium (137 mmol/L) were within normal limits. With the exception of a small haemangioma located in the left cerebellar lobe, no pathological changes on magnetic resonance imaging of the brain and pituitary were found. Adiponectin concentration (10.2  $\mu$ g/mL) was lower than in patients with alimentary-induced obesity (18.0  $\pm$  2.5  $\mu$ g/mL). Ghrelin (49.4 ng/mL), obestatin (115.6 ng/mL), peptide YY (10.0 ng/mL), neuropeptide Y (750.8 ng/mL), glucagon-like peptide-1 (51.5 pg/mL), insulin (14.8 mIU/L), resistin (4.5 ng/mL), and leptin (21.2 ng/mL) levels did not differ from those observed previously in patients with simple obesity, treated in our departments. Administration of piracetam (4.8 g/day) partially improved the patient's general feeling and reduced intensity of complaints. Our eight-month trial of a treatment with orlistat (360 mg/daily in three doses) plus sibutramine (15 mg/day once daily), combined with lifestyle modification and behavioural therapy, resulted in only a small (about 5%) and transient reduction of body mass. The lack of success of traditional therapy made the patient decide to undertake bariatric surgery treatment with a Roux-en-Y gastric bypass. Although a 10% reduction in body weight was observed during the first 6 months after operation, presently the patient's weight is almost 18% below the maximal weight. Because of the risk of iron deficiency, vitamin B12 deficiency, and impaired vitamin D and calcium absorption, the patient is supplemented with these nutrients. Apart from occasional diarrhoea, no other side effects of the bariatric intervention are reported. Her body mass is 73 kg, BMI 25.6 kg/m<sup>2</sup>, and waist circumference 94 cm. Although she still experiences periodic headaches, dizziness, diaphoresis, insomnia, depressive moods, and reduced libido, the frequency and intensity of these symptoms is significantly less than previously.

## Discussion

Pregnancy is associated with an increased secretion of tropic hormones, leading to enhanced sensitivity of the

hypothalamic cells to ischaemia [7]. If, during pregnancy or labour, the blood supply is disturbed by a significant loss of blood, metabolically active cells within this region may become transiently or persistently damaged [2]. This was the case in our subject, who underwent a long delivery with a massive haemorrhage.

Interestingly, no significant changes in the secretion of prolactin and activity of the GH-IGF-1, hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-ovarian axes were observed. This finding clearly indicates that neither obesity nor other complaints experienced by the patient can be explained by abnormal hormonal secretion. This possibly means that either the destruction was limited to the hypothalamic regions involved in body mass control, or, and this explanation is more probably, the mechanisms responsible for the regulation of energy balance are more prone to ischaemic destruction than those controlling hormone synthesis and release. Therefore, probably no therapy targeted at these endocrine systems would bring benefits to this individual.

It should be stressed that, despite hypothalamic dysfunction, the patient managed to conceive within a short period of time from her previous pregnancy. This finding indicates that the presence of hypothalamic dysfunction does not disqualify a patient from having children. However, as the reported case shows, the subsequent pregnancies and deliveries may exacerbate the clinical course of this disease. Our patient responded only weakly to the therapy with sibutramine and orlistat, even in the case when these agents were administered in combination at their highest doses together with non-pharmacological means of treatment (a low-caloric diet, physical exercise, and behavioural therapy). A visible effect was observed only after performing a Roux-en-Y gastric bypass. This finding supports the previous observations that bariatric surgery is the most effective means of treatment of drug-resistant obesity, associated with an acceptable number of adverse effects [8, 9]. Although bariatric surgery is recommended for subjects with BMI exceeding 35 kg/m<sup>2</sup> [8, 9], our results also evidenced its benefits in individuals with less severe obesity coexisting with other disturbances.

Piracetam, the most commonly used nootropic drug, being a cyclic derivative of gamma-aminobutyric acid, administered at high doses reduced some symptoms in our patient (drowsiness, flushing, diaphoresis) and restored the correct eating and thirst behaviours. These benefits may be attributed to piracetam-induced changes in the physical properties of the plasma membrane caused by increasing its fluidity and protecting the cell against hypoxia, which is responsible for the antithrombotic, neuroprotective, and rheological properties of this agent [10].

Our study is the first one to investigate plasma levels of hormones involved in the regulation of food intake in patients with postpartum hypothalamic dysfunction [11]. In the study, ghrelin, glucagon-like peptide-1, obestatin, peptide YY, neuropeptide Y, and leptin levels remained at a similar level as those in patients with alimentary obesity. This suggests that either hypothalamic dysfunction does not affect the release of these hormones, or plasma levels of ghrelin, glucagon-like peptide-1, obestatin, peptide YY, neuropeptide Y, and leptin do not accurately reflect their local concentrations in the central nervous system. However, because hormonal analysis was performed only at baseline conditions, we cannot exclude the existence of disturbances in the postprandial secretion of these hormones. The only exception was the very low level of adiponectin, which suggests that this hormone may contribute to the pathogenesis of postpartum hypothalamic dysfunction. If so, adiponectin-targeted drugs, being the subject of intense research [12], may provide some benefits to patients with obesity induced by abnormal functioning of the hypothalamus. Our study design did not allow us to exclude the association between postpartum hypothalamic dysfunction and abnormal functioning of the endocannabinoid, proopiomelanocortin, serotonergic, and other systems in-

involved in the regulation of food intake and energy expenditure, which is an interesting direction for further research on patients with this disease.

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