HYPOPHISITIS IN PREGNANT WOMEN WITH PERSISTENT DIABETES INSIPIDUS IN THE OUTCOME

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Autoimmune/lymphocytic hypophysitis is one of the rare causes of central diabetes insipidus in adults and is most common among women in the second or third trimester of pregnancy. Numerous studies have shown that lymphocytic hypophysitis is characterized by a very variable clinical signs with the development of neurological symptoms, visual disturbances and hypopituitarism with partial or complete loss of pituitary function, as well as a number of features in magnetic resonance imaging (MRI). Isolated lymphocytic indibuloneurohypophysitis occurs in fewer cases and involves the posterior lobe and stalk of the pituitary gland with a clinical presentation of diabetes insipidus. The above clinical case describes the development of hypophysitis in a pregnant woman with a predominant lesion of the posterior pituitary gland and an outcome in diabetes insipidus, which persists 6 years after pregnancy and childbirth. In the article some aspects of the differential diagnosis of diabetes insipidus in pregnant women, as well as instrumental diagnosis and treatment approaches of hypophysitis are discussed.

KEYWORDS: central diabetes insipidus; pregnancy; lymphocytic hypophysitis.

ГИПОФИЗИТ ВО ВРЕМЯ БЕРЕМЕННОСТИ С ИСХОДОМ В СТОЙКИЙ НЕСАХАРНЫЙ ДИАБЕТ

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Аутоиммунный/лимфоцитарный гипофизит является одной из редких причин развития центрального несахарного диабета у взрослых пациентов и наиболее часто встречается среди женщин во втором или третьем триместрах беременности.

В многочисленных исследованиях показано, что лимфоцитарный гипофизит характеризуется весьма вариабельной клинической картиной с развитием неврологической симптоматики, нарушений со стороны зрения и гипопитуитаризма с частичным или полным выпадением функций гипофиза, а также рядом особенностей при магнитно-резонансной томографии (МРТ).

Изолированный лимфоцитарный инфудибулонейрогипофизит встречается значительно реже и затрагивает заднюю долю и ножку гипофиза с клинической картиной несахарного диабета.

В приведенном клиническом случае описывается развитие гипофизита у беременной пациентки с преимущественным поражением задней доли гипофиза и исходом в несахарный диабет, сохраняющимся через 6 лет после беременности и родов.

В статье рассмотрены аспекты дифференциальной диагностики несахарного диабета у беременных, а также особенности инструментальной диагностики и подходов к лечению гипофизита.

КЛЮЧЕВЫЕ СЛОВА: центральный несахарный диабет; беременность; лимфоцитарный гипофизит.

BACKGROUND

Diabetes insipidus (DI) in pregnancy is a relatively rare condition with a prevalence of approximately 2–6 cases per 100,000 pregnant patients [1].

It is known that diabetes insipidus (DI) in pregnant women can develop as a result of increased activity of the vasopressinase enzyme secreted by the placenta, so-called gestational diabetes insipidus; somewhat less frequently it can result from various pathological processes in the brain (central diabetes insipidus, CDI) or renal vasopressin resistance (nephrogenic diabetes insipidus) [2].

Of particular interest are cases of central diabetes insipidus in pregnant women secondary to autoimmune (lymphocytic) hypophysitis, usually characterised by partial or complete loss of anterior and/or posterior pituitary function, as well as a number of neurological and ophthalmological disorders [3].

This case report describes development of hypophysitis in a pregnant patient with predominantly posterior pituitary lobe involvement and outcome in diabetes insipidus persisting six years after pregnancy and delivery. This clinical example is a case of interest because in the majority of previously described cases of hypophysitis in pregnant women, persistent dysfunction of anterior or both anterior and posterior pituitary lobes was observed [4–8], whereas isolated posterior lobe involvement with infundibuloneurohypophysitis and, as a consequence, diabetes insipidus has occurred much less frequently [9, 10]. This fact requires greater awareness among endocrinologists, obstetricians

Received: 19.10.2023. Accepted: 21.11.2023.

and gynaecologists about possible clinical, laboratory and instrumental markers of hypophysitis and approaches to its treatment.

CASE REPORT

Female patient U., 26, first came to Russia's Endocrinology Research Centre in 2017 at 20th–21st week of pregnancy with complaints of pronounced polydipsia (consuming up to 6.0–6.5 litres of fluid per day), frequent copious urination with excretion of up to 6.0 litres of fluid per day, and nycturia.

The patient's medical history stated that from the 14th week of pregnancy she had been disturbed by pronounced headaches of the "hoop" type and a sensation of "pulsation in the right eye socket". A neurologist prescribed triptanes and her headaches were briefly relieved. Later, the patient noticed an eyelid oedema on the right side, and an ophthalmologist's examination revealed a decrease in visual acuity of the right eye and binasal narrowing of visual fields.

During the examination for headaches and visual disturbances at 17th–18th week of pregnancy, the patient underwent non-contrast brain MRI, which revealed a 10×15×20 mm pituitary adenoma with suprasellar growth and moderate

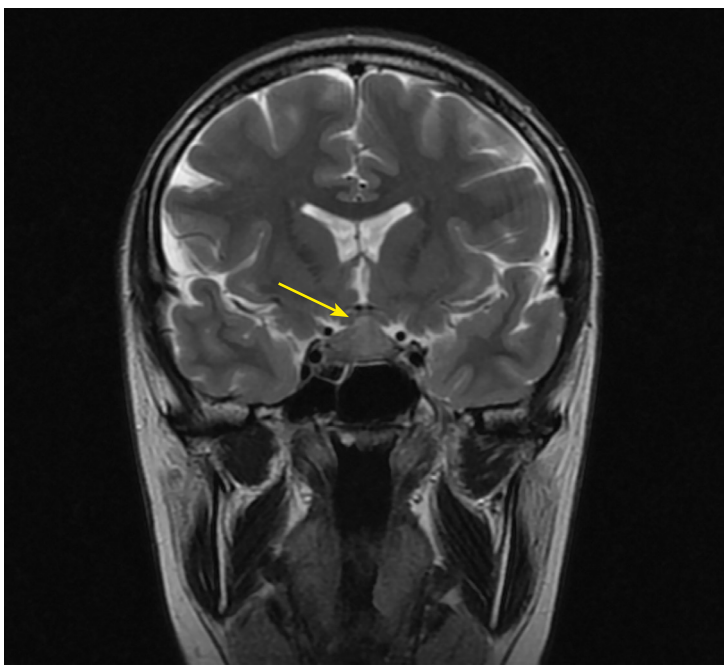

Figure 1: Non-contrast MRI of the head, T2 WI, coronal (frontal) projection. MR picture of an "adenoma" of the pituitary gland measuring 10×15×20 mm with suprasellar growth and moderate compression of the chiasma (changes are indicated with an arrow).

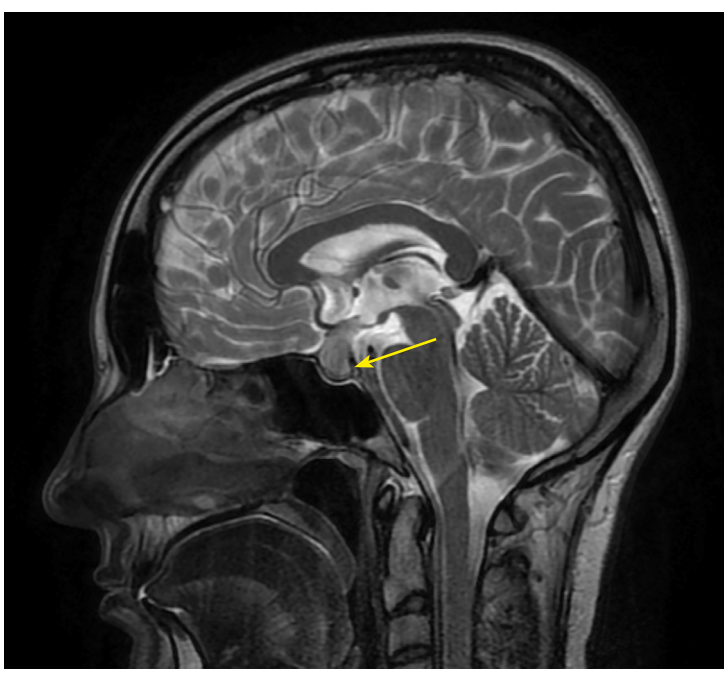

Figure 2: Non-contrast MRI of the head, T2 WI, sagittal projection. Posterior pituitary is not differentiated (changes indicated by arrow).

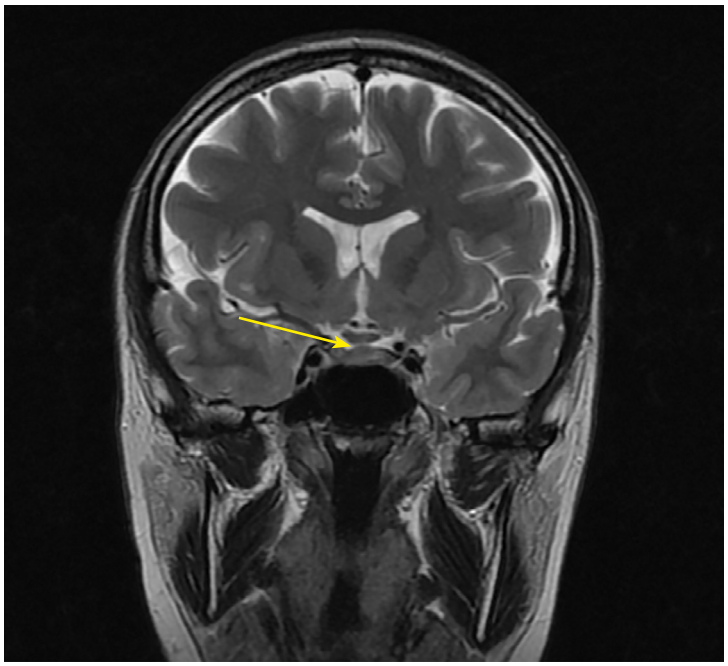

Figure 3: Non-contrast MRI of the head, T2 WI, coronal (frontal) projection. Thickening of the pituitary stalk is preserved (changes are indicated by the arrow).

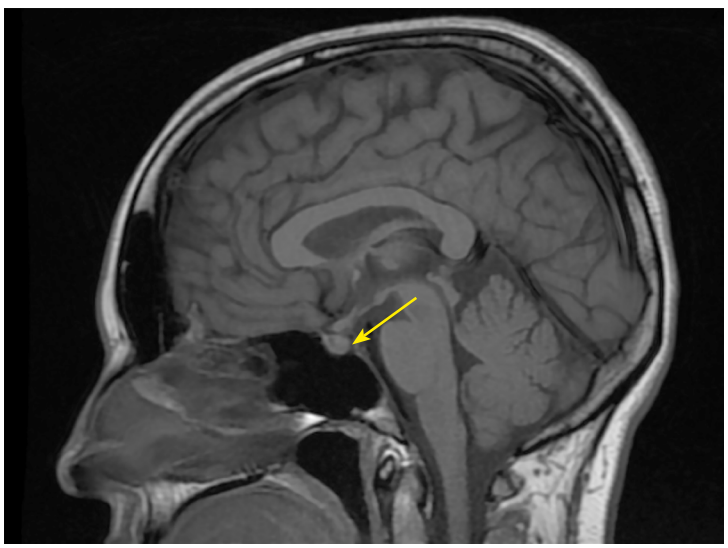

Figure 4: Non-contrast MRI of the head, T1 WI, sagittal projection. Posterior pituitary is not differentiated (changes indicated by arrow).

compression of the chiasma; posterior pituitary was not differentiated (Figures 1, 2).

Due to persisting headaches and eyelid oedema on the right side, the patient independently initiated dexamethasone therapy 4–8 mg intramuscularly once every three days from 19th–20th week of pregnancy. Dexamethasone treatment resulted in decreased eyelid oedema, improved vision, and headaches relief. When re-examined by an ophthalmologist several weeks later, no ophthalmological abnormalities were detected.

At 18th–19th week of pregnancy, the patient first noted increased polydipsia and frequent, profuse urination. Diabetes mellitus (DM) was ruled out, and when the patient was examined at the 18th week of pregnancy, fasting glycaemia was less than 5.1 mmol/L. The urinalysis showed a low relative density (1,000 g/L). However, the results of hormonal examination could not exclude the development of secondary hypothyroidism and secondary hypocortisolism: TSH at 0.022 mIU/L (0.4–4.0), free T4 at 9.12 pmol/L (9.0–19.0), basal cortisol at 39 nmol/L (101–535); the patient did not consult a doctor with regard to the findings of that examination.

At her first visit to Russia's Endocrinology Research Centre (at 20th–21st week of pregnancy), the patient underwent a repeated hormonal study which revealed no signs of secondary hypothyroidism and hypocortisolism: TSH at 1.89 mIU/L (0.4–4.0), free T4 at 12.9 pmol/L (11.5–22.7), basal ACTH at 14.2 pg/ml (0.0–46.0), basal cortisol at 564 nmol/l (101–535), while urine relative density remained low at 1,000 g/L. An oral glucose tolerance test performed at the 24th week of pregnancy showed no evidence of carbohydrate metabolism disorder.

During dexamethasone therapy, brain MRI showed a regression of changes in the chiasmal-sellar region with

thickening of the pituitary funnel and lack of signal from the posterior pituitary (Figures 3, 4).

The MR picture, medical history and the patient's persisting complaints of polydipsia and profuse, frequent urination, allowed to evaluate the patient`s condition as hypophysitis with development of diabetes insipidus. The patient was recommended to take desmopressin 30 μg sublingual pills twice a day; during this treatment she reported a significant improvement in her condition, fluid intake and urination normalisation. Later, she independently reduced the desmopressin dose to 15 μg twice a day.

Preterm labour began at the 35th–36th week. The neurosurgeon's recommendation to perform C-section was followed, and a boy was born, 7/7 Apgar score, weight 2,120 g, body length 42 cm. At the first examination, signs of prematurity were observed; respiratory and heartbeat parameters were within normal range. In the early neonatal period, the baby developed hypoglycaemia (clinically: atony, weak sucking reflex), most likely due to the patient's independently continued dexamethasone therapy (intramuscular injections) until delivery, and to premature pregnancy. Intravenous administration of 5% glucose solution was carried out. Lactation was terminated with dopamine agonists soon after delivery on the patient's request. Regular menstrual cycle was restored one month after delivery and has lasted to date.

The patient returned to Russia's Endocrinology Research Centre six years after childbirth in June 2023. At this time,

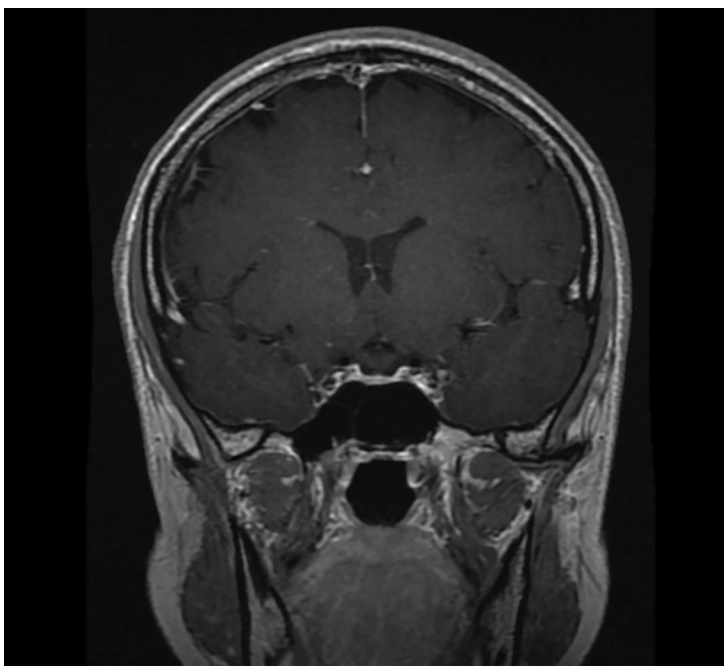

Figure 5: Non-contrast MRI of the head, T1 WI, coronal (frontal) projection. MR picture of partially "empty" Turkish saddle.

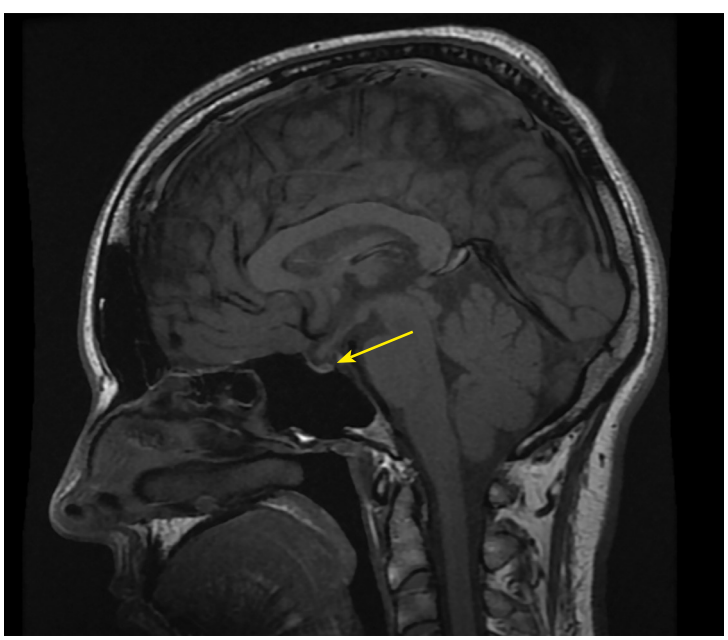

Figure 6: Non-contrast MRI of the head, T1 WI, sagittal projection. MR picture of partially "empty" Turkish saddle. No signal from posterior pituitary (changes indicated by arrow).

she was taking 15 μg desmopressin twice a day. The purpose was to confirm diabetes insipidus, exclude hypopituitarism and correct the therapy.

During the examination, when skipping the evening dose of desmopressin and restricting fluid intake after 21:00, morning blood tests revealed hypernatremia (blood sodium at 148.4 mmol/L (136.0–145.0 mmol/L), increased plasma osmolality at 302 mOsmol/kg (280–300 mOsmol/kg) with low urine osmolality at 302 mOsmol/kg (300–1200 mOsmol/kg), which confirmed CDI, and desmopressin therapy was resumed.

Secondary adrenal insufficiency (basal cortisol at 663 nmol/L (171–536), basal ACTH at 78 pg/ml) and secondary hypothyroidism (free T4 at 12.3 pmol/L (9-19), TSH at 0.83 mIU/L (0.25–3.5)) were excluded.

Brain MRI with contrast revealed a picture of a partially «empty sella syndrome» and no signal from posterior pituitary. Thus, central genesis of persisting diabetes insipidus was confirmed (Figures 5, 6).

Moreover, additional examination of the patient six years after delivery enabled timely detection of a malignant thyroid neoplasm (papillary cancer, classical subtype, pT1bN0M0) and surgical treatment (right-side hemithyroidectomy).

Thus, based on the results of the examination, the following diagnosis was made:

Central diabetes insipidus in the outcome of hypophysitis associated with pregnancy , drug compensation. Right-sided hemithyroidectomy for adenocarcinoma pT1bN0M0. Left-sided nodular goitre, Grade 0 (WHO).

Due to improved condition with administration of 15 μg desmopressin twice a day the patient was recommended to continue the therapy in the same dose and maintain an adequate liquid consumption regime. The patient was discharged and prescribed to undergo regular follow-up checks with an endocrinologist.

DISCUSSION

In 1942, H. Blotner and P. Kunkel described some of the earliest cases of diabetes insipidus in pregnancy, including reports dated 1790s [11]. Decades of observation have shown that there are many causes for the development of DI during pregnancy. As stated earlier, DI during gestation often develops as a result of increased activity of vasopressinase secreted by the placenta, in which case it is called gestational diabetes insipidus, but it can also result from various pathological processes in the brain (central diabetes insipidus) or renal vasopressin resistance (nephrogenic diabetes insipidus) [2].

Gestational DI in pregnant women (GDI), also known as transient DI, is the most common DI type during pregnancy [12]. In GDI, typical symptoms (polyuria, polydipsia) usually occur in the first trimester, but more often peak in the late second or third trimester of pregnancy as the placenta matures and gains weight. The pathogenesis of GDI is due to an increase in placental vasopressinase levels, which causes an 80%–85% decrease in circulating vasopressin (antidiuretic hormone, ADH) [13] and development of DI. Typically, all symptoms cease shortly after delivery [14]. In addition to increased vasopressinase activity, anterior pituitary physiological hypertrophy and hyperplasia in pregnancy may lead to compression of posterior pituitary and decreased ADH levels. In, some cases liver disease also complicates pregnancy (*e.g.*, acute fatty liver dystrophy, HELLP syndrome), and impaired hepatic deactivation of vasopressinase also leads to decreased ADH levels [15].

Nevertheless, it should be noted that GDI is a rare condition and requires differential diagnosis with other causes of DI in pregnant women [16].

Thus, central DI (CDI) in pregnancy develops as a result of insufficient synthesis and/or release of ADH and may manifest during pregnancy due to an increased need for ADH. While GDI usually does not manifest clinically until the 2nd and 3rd trimesters when placental vasopressinase levels peak, CDI should be suspected when signs and symptoms of DI appear earlier in pregnancy [1]. The causes of CDI in pregnancy may vary from genetic syndromes (e.g., Wolfram syndrome) to acquired forms (brain injury, surgery, autoimmune (lymphocytic hypophysitis), infiltrative, neoplastic and infectious processes in the pituitary gland and hypothalamus) [17]. In rare cases, postpartum DI is also detected as part of the Sheehan syndrome, associated with ischaemic processes in a hyperplasic pituitary gland after blood loss during labour [18].

Nephrogenic DI (NDI) in pregnancy develops due to renal insensitivity to ADH and, like CDI, may manifest during pregnancy due to an increased need for ADH. Genetic and acquired causes may underlie NDI. For example, an X-linked recessive mutation of *AVPR2* gene on Xq28 chromosome accounts for 90% of instances of hereditary nephrogenic diabetes insipidus [19]. Clinical presentation in women can vary from asymptomatic mutation carrier to subclinical DI. Other hereditary and acquired renal diseases can also lead to manifestation of nephrogenic DI during pregnancy [1, 20].

Approaches to the treatment of gestational and central diabetes insipidus in pregnant women do not differ significantly and include therapy with desmopressin (which is vasopressinase-resistant, as opposed to endogenous vasopressin). As to the therapy of nephrogenic DI in pregnant women, it usually consists of finding and eliminating the cause of DI [1].

In the described case, specific clinical picture and medical history, response to glucocorticoid and desmopressin treatment, as well as MRI changes allowed to suggest CDI which had developed as a result of autoimmune hypophysitis.

Hypophysitis is a rare disease of the pituitary gland characterised by non-neoplastic infiltration of its tissue and increased pituitary gland size, leading to impairment of its functions. The prevalence of hypophysitis is estimated as one new case per 7–9 million population per year [21]. Primary hypophysitis is caused by autoimmune inflammation of the pituitary gland, as opposed to secondary hypophysitis which is caused by systemic diseases or medications [22].

Autoimmune hypophysitis is one of the forms of the disease. It is characterised by infiltration of pituitary tissue by lymphocytes, plasma cells, eosinophils, macrophages and neutrophils, which leads to fibrous dystrophy of glandular parenchyma and is accompanied by pituitary gland dysfunction of various severity [23].

Development of autoimmune hypophysitis is in many cases associated with pregnancy and labour, and clinical symptoms are particularly observed in the 2nd or 3rd trimester of pregnancy or in the first two months postpartum;

however, lymphocytic hypophysitis may potentially manifest at any time during pregnancy [3].

The most common form of autoimmune hypophysitis is lymphocytic one [24]. For a long time, the terms autoimmune and lymphocytic hypophysitis were considered synonymous [25]. However, a growing understanding of histological differences in hypophysitis has made it clear that lymphocytic hypophysitis is actually just one of the types of autoimmune hypophysitis. Other types include granulomatous, xanthomatous, necrotising, IgG4-mediated and drug-induced hypophysitis [24]. Since the vast majority of cases of autoimmune hypophysitis are lymphocytic, the two terms are often used interchangeably in the literature [25].

Hypophysitis may affect anterior pituitary (adenohypophysitis, 65% of all cases) causing a loss of its functions; it may affect posterior pituitary and the stalk (infundibuloneurohypophysitis, 10% of cases) or involve the entire pituitary gland (panhypophysitis, 25% of cases). Thus, clinical picture of lymphocytic hypophysitis is highly variable [3]. E. Thodou *et al.* in 1995 described 16 patients with lymphocytic hypophysitis, and in 63% of cases they observed dysfunction of anterior pituitary; in 56% of cases they reported visual field disturbance and headaches (as a consequence of mass effect), in 38% – hyperprolactinaemia, and in 19% of patients – development of DI [26]. According to another study involving 492 patients, various manifestations of mass effect (headaches or visual disturbances, paresis of III, IV or VI pairs of cranial nerves) were the most frequent (58%); symptoms of hypopituitarism were also observed (44%); DI was detected in 31% of cases, and hyperprolactinaemia in 18% of cases [27].

When it comes to hypopituitarism in lymphocytic adenohypophysitis, secondary adrenal insufficiency is most frequently detected; the other most common disturbances include TSH, gonadotropic hormones, and prolactin deficiencies [3].

As mentioned earlier, lymphocytic infundibuloneurohypophysitis affects predominantly the posterior pituitary lobe and pituitary stalk; it is associated with DI clinical picture and occurs much less frequently than adenohypophysitis [2].

Probably, it is the form of hypophysitis that was observed in the patient described above; however, the patient's tests showed low level of basal cortisol, low-to-normal level of free T4 and reduced level of TSH, so we cannot exclude the involvement of anterior pituitary in the pathological process (probably, to a lesser extent), which, nevertheless, was transient. We ought to mention some limitations of hormonal tests interpretation in this case. The TSH level decrease could be a consequence of a transient thyrotoxicosis in the first trimester (the patient did not provide any data on her TSH level in the first trimester). However, the persistence of low TSH levels by the 18th–19th weeks of pregnancy, especially with low-to-normal levels of free T4, still suggests a secondary hypothyroidism. Although no reference intervals for basal cortisol have been established for pregnant patients, a significantly reduced cortisol baseline (39.0 nmol/L) also indicates probable transient secondary hypocortisolism.

Most often, infundibuloneurohypophysitis progresses from inflammation to fibrosis and subsequent atrophy of posterior pituitary tissue, which eventually manifests as the "empty sella syndrome" with persistent hypopituitarism/DI [28].

The specific MRI picture in hypophysitis is a symmetrical increase in pituitary volume (due to the its size increase), diffuse irregularity of signal from anterior pituitary tissue, varying-degree cystic changes in the anterior pituitary structure and active accumulation of contrast agent by the adjacent dura mater with the formation of dural tail sign. In some cases, changes in the structure of the chiasma and visual tracts may be observed (hyperintense MR-signal on T2 WI) [22].

When posterior pituitary is involved in the pathological process, oedema, thickening of the pituitary stalk >3 mm at the level of the hypothalamic median eminence, and loss of the hyperintense signal from posterior pituitary are usually detected [29]. It is known that MRI picture in hypophysitis is often interpreted as a mass lesion in the pituitary gland. A. Gutenberg *et al.* developed a radiological scale to distinguish autoimmune hypophysitis from pituitary adenomas and identified 8 significant predictors that would enable us correctly to distinguish between these two conditions [29]. The symptoms manifestation in later pregnancy stages, an enlarged and homogeneous pituitary gland in the pre-contrast phase, the loss of signal from posterior pituitary, and pituitary stalk thickening are all in favour of hypophysitis [25, 30]; however, these indicators are not always specific, and some of them may also occur in mass lesions and infiltrative processes of the chiasmal-sellar region, which poses certain diagnostic pitfalls [3]. In the above case, MR images initially described a mass lesion in the chiasmal-sellar region, which, as mentioned above, can also be observed in hypophysitis, but at the same time the features specific to hypophysitis (pituitary stalk thickening and persistent absence of signal from posterior pituitary) were observed.

Biopsy of the pituitary gland is the most reliable way to diagnose lymphocytic hypophysitis; however, this method is invasive and is performed only in selected cases when the diagnosis is doubtful and the biopsy findings may affect the treatment strategy [2]. If no indications for surgical treatment exist, the diagnosis of hypophysitis is based on clinical, laboratory, and radiological findings [22].

There have been multiple attempts to identify and to use in practice some antibodies specific for autoimmune hypophysitis as an additional diagnostic marker of the disease [3]. Thus, in 2015. S. Iwama *et al.* [31] and K. Sakurai *et al.* [32] attempted to use antibodies to rabphilin-3A as a marker of lymphocytic infundibuloneurohypophysitis with the development of DI in the third trimester of pregnancy. However, investigation of antibody titres to rabphilin-3A and other anti-pituitary antibodies is still limited in clinical practice.

Most cases of lymphocytic hypophysitis are self-resolving with spontaneous disappearance of ophthalmological and neurological symptoms associated with compression of the sella turcica structures. However, many patients require long-term replacement therapy for hypopituitarism [33]. Treatment of hypophysitis is predominantly includes replacing the lost pituitary functions and/or managing the mass effect symptoms (headaches, visual disturbances, cranial nerve paresis) [25]. Pulse therapy with glucocorticoids is most often used in hypophysitis with severe headaches, visual disturbances and hypopituitarism, leading to restoration of the function of the pituitary gland anterior

and posterior lobes, reduction of oedema in the sellar region and pituitary stalk [34]. Other immunosuppressors (rituximab, azathioprine, methotrexate and cyclosporine A) have also demonstrated efficacy in hypophysitis in some cases [24, 35]. Surgical treatment is usually considered in severe or life-threatening cases with pronounced visual field impairment, cranial nerve paresis, or in lack of response to medication treatment [36]. With medication treatment, recovery of pituitary function occurs in 27% of cases, and radiological regression is observed in 46% of cases [3].

Thus, in the case described above, a specific clinical picture with ophthalmological abnormalities, severe headaches, which were resolved through dexamethasone therapy, and, of course, the development of isolated persistent DI in combination with specific MRI changes, *i.e.*, the loss of signal from posterior pituitary suggest infundibuloneurohypophysitis during pregnancy.

CONCLUSION

The described clinical case demonstrates a rare type of hypophysitis in pregnancy with isolated persistent dysfunction of posterior pituitary and development of CDI. Hypophysitis should be taken into account as one of the possible causes of hypopituitarism in pregnant patients, and in all cases pituitary tropic hormone deficiency should be excluded, since undetected secondary adrenal insufficiency and secondary hypothyroidism may threaten to mother`s and child`s life during or after delivery. Knowledge of MR-diagnostic features and treatment approaches in hypophysitis enables one to avoid unnecessary surgical treatment of pituitary masses, which is especially important in the management of pregnant patients. Certain diagnostic pitfalls and low prevalence of hypophysitis among pregnant women require high awareness among endocrinologists, obstetricians and gynaecologists regarding this disease course, diagnosis and treatment.

ADDITIONAL INFORMATION

Source of funding. The patient's examination and treatment were paid for from funds allocated by Grant 121030100034-1 "Endocrine-mediated disorders of osmotic homeostasis: Studies in etiological and pathogenetic factors, development of personalised approaches to differential diagnosis".

Conflict of interest. The authors hereby declare they have had no apparent or potential conflict of interest related to the content of this publication.

Authors' contribution. Every author has approved the final version of the text prior to publication and agreed to accept responsibility for all aspects of this study, which implies due investigation and resolution of any issue related to the accuracy or integrity of any part thereof.

Patient's consent. The patient has voluntarily given her informed consent for the publication of her personal medical information in anonymised form.

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Manuscript received: 19.10.2023. Approved for publication: 21.11.2023. Published online: 30.08.2024.

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TO CITE THIS ARTICLE:

Dzeranova LK, Pigarova EA, Vorotnikova SY, Voznesenskaya AA. Hypophisitis in pregnant women with persistent diabetes insipidus in the outcome. *Problems of Endocrinology*. 2024;70(4):15-23. doi: https://doi.org/10.14341/probl13384