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[1]Department of Gynecology, Obstetrics and Neonatology, University of Parma
[2]European Gynaecology Endoscopy School, Sacred Heart Hospital, Negrar, Verona
Department of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome
Department of Gynecology and Obstetrics, S. Orsola Hospital, University of Bologna
[3]Department of Human Anatomy, Medical University of Lublin

ROBERTO BERRETTA[1], SALVATORE ANFUSO[1],
MARCELLO CECCARONI[2], MARTINO ROLLA[1],
RYSZARD MACIEJEWSKI[3] ALBERTO BACCHI MODENA[1]

# *A case report of the Sheehan's syndrome with acute onset, hyponatremia and severe anemia*

Sheehan's syndrome, first described by Sheehan in 1937 (1), is a well-known cause of panhypopituitarism secondary to pituitary apoplexy. This syndrome generally occurs after an intra- or postpartum bleeding episode characterized by severe hypertension or hemorrhagic shock. Vasospasm, thrombosis and vascular compression of the hypophyseal arteries have also been described as possible causes of the syndrome. Some authors believe that the Sheehan's syndrome may occur even in the absence of any detectable postpartum hemorrhage, but this seems to be a very rare occurrence.

Although the pathogenesis of the Sheehan's syndrome is not entirely clear, the primary causative factor is a widespread ischemic lesion of the pituitary gland resulting in the impairment of anterior pituitary function.

The pituitary gland is particularly vulnerable to necrosis from any vascular compromise that may arise during pregnancy, especially in the peripartum period. During pregnancy, the pituitary gland undergoes remarkable changes in volume as a consequence of hyperplasia – a process triggered by placental estrogen secretion, which involves the prolactin-secreting cells of the pituitary gland (so-called "pituitary lactotrope cells"). As supporting evidence, Gonzalez et al. (2) reported an MRI-verified increase of 136% in pituitary volume compared with controls. However, the increased pituitary volume is not accompanied by a corresponding increase in vascular supply through the portal system, because the pituitary gland cannot expand out of its bone cavity in the sella turcica. As a result, hypertension or vasospasm in the hypophyseal arteries, or an insufficient vascularization of the gland tissue, may irreversibly damage arterial circulation to the adenohypophysis. The extent of pituitary necrosis determines whether the onset of the Sheehan's syndrome will be earlier or later and also affects the degree of pituitary functional impairment. However, the pituitary gland has very good reserve capabilities, meaning that more than 75% of tissue needs to be compromised before any clinical manifestations of the syndrome occur. In certain cases, patients will completely recover their pituitary function. Moreover, variable degrees of hypopituitarism are recognized, ranging from a single hormone deficiency to a general disorder.

Based on such evidence, it is clear that the onset of the Sheehan's syndrome may vary widely in different patients. However, in most cases, the syndrome sets in several months or even years after a delivery complicated by severe hemorrhage. Therefore, it is often misrecognized and not adequately treated, and in some patients its onset is so abruptly severe as to lead to coma and eventually death.

In a study conducted by Sert et al. (3) on 28 cases with Sheehan's syndrome, the disease was diagnosed on average after 13.92 years from its primary obstetric cause. Hence, the importance of early diagnosis to start adequate hormone replacement therapy as soon as possible. Generally, the presenting symptoms in patients with Sheehan's syndrome may range from totally non-specific to more or less specific to comatose. In certain cases, it is a stressful event that precipitates onset and enables the diagnosis. However, the most common presenting symptoms of complete panhypopituitarism are lack of lactation (due to decreased serum prolactin concentrations) and involution of the mammary gland. Subsequent symptoms include lack of return of menstruation and lack of pubic an axillary hair growth, due to the deficit in gonadotropin synthesis and secretion. Finally, signs and symptoms of hypothyroidism and hypoadrenalism progressively set in. According to Sert et al. (3), while only a few women reported the lack of return of menstruation and of lactation, all of them had hypothyroidism, hypoadrenalism and growth hormone (GH) deficiency. These findings suggest a different timing for the onset of hormone deficiency, depending on the degree of impairment in pituitary function. The possible onset of diabetes insipidus has also been described in about 5% of patients. Some authors observed baseline antidiuretic hormone (ADH) deficiencies and impaired responses of ADH to an osmolar load in most patients. In addition, the appearance of diabetes insipidus in patients with Sheehan's syndrome has been described during subsequent gonadotropin-induced pregnancies

Diagnosis of the Sheehan's syndrome is based on the patient's history and observation, on laboratory tests – including hormone levels and hormone stimulation tests – and on CT scans or, preferably, MRI scans. Lab tests will reveal panhypopituitarism with low thyroxine, estradiol, and cortisol levels, and with inadequately low levels of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and adrenocorticotropic hormone (ACTH). Frequently, lab tests will also reveal hyponatremia, which occurs in 33% to 69% of cases and represents the most common electrolytic disorder in the Sheehan's syndrome (3). Hyponatremia has a late onset and can be induced by different causes, such as volume depletion, cortisol deficiency, hypothyroidism, or a syndrome characterized by ADH insufficiency. By contrast, hyponatremia is rarely observed in the early postpartum period as a direct consequence of panhypopituitarism.

The MRI study of the pituitary gland may reveal different features depending on the stage of the disease. While early scans demonstrate a non-hemorrhagic enlargement of the pituitary gland leading to its subsequent involution, late scans typically show an empty sella. A secondary empty sella is considered a characteristic finding in the classical form of the Sheehan's syndrome (1). However, very few observations of CT or MRI features in the acute phase are available. Hormone replacement therapy, with careful follow-up of laboratory and clinical results, is the treatment of choice.

In the literature there are only few reports on the early diagnosis of acute-onset cases with severe signs and symptoms. Published cases with early MRI scans are also few in number. We report the case of a woman with and early diagnosis of the early-onset Sheehan's syndrome associated with severe hyponatremia and severe patient compromise, following dystocic childbirth complicated by postpartum hemorrhage.

## CASE HISTORY

A 35-year-old woman from Italy presented to the emergency department of our hospital in January 2005 because on the eighth day after delivery she began complaining of asthenia associated with abdominal pain and cramps in the lower limbs, preceded by persistent headache. In addition, the patient reported lack of milk secretion after childbirth.

Based on her previous medical history, it appeared that the woman had had an uncomplicated pregnancy ending in spontaneous labour at 39.5 weeks' gestational age. Although the fetal heart rate pattern during labour was normal according to the American College of Obstetricians and Gynecologist (ACOG) guidelines, delivery was dystocic due to the appearance of marked uterine hypokinesia that required the application of a new-generation vacuum extractor. A baby boy was delivered, who had an Apgar score of 10 at 1' and weighed 3200 g, which was adequate for gestational age according to the birth weight curves used in our hospital's maternity unit. The postpartum period was complicated by a significant blood loss of 500 mL from uterine atony. The patient and the baby were discharged from hospital 48 hs after delivery.

Upon her re-admission to hospital, the patient's vital parameters were in the normal range. The laboratory tests showed a normocytic normochromic anemia with low hemoglobin (HGB) concentration (8.8 g/dL), low red-blood cell (RBC) count (3.06 x $10^6$/μL] and low hematocrit (HCT) levels (24.9%); a thrombocytosis with platelet (PLT) count (516 x $10^3$/μL); a slight glutamic oxaloacetic transaminase (GOT) elevation (63 IU/L); low $Na^+$ levels (108 mEq/L) and low $Cl^-$ levels (83 mEq/L). The remaining tests were in the normal range. Based on the results of the laboratory tests, the patient received an intravenous infusion of 50cc saline with 0.5 mEq of $Na^+Cl^-$, followed by another IV saline infusion of 25 mg/h of hydrocortisone. The patient was later moved to our hospital's Department of Gynecology, Obstetrics and Neonatology, where she had additional blood tests and an endocrinological assessment based on a clinical examination and other laboratory tests. The patient also underwent an MRI of the brain and of the facial bones.

The tests confirmed the patient's state at admission. Hormone levels were as follows: ACTH, <5.00 pg/mL (normal range [9–52 ng/l.], 0–46); TSH, 0.282 μU/mL (n.r., 0.400–4.000); free triiodothyronine (FT3), 1.32 pg/mL (n.r., 1.80–4.80); free thyroxine FT4, 1.30 ng/dL (n.r., 0.80–1.90); FSH and LH, <0.10 mUI/mL (n.r.,... ); prolactin (PRL), 3.57 ng/mL (n.r., 3.50–30.00); and ADH, 2.9 pg/mL (n.r., 0.0–6.7).

On MRI scanning, the adenohypophysis showed a basically normal signal in the images taken before contrast medium injection, as opposed to abnormal lack of enhancement after contrast medium injection.

Treatment was based on administration of saline with the addition of NaCl, hydrocortisone, levothyroxine sodium, ranitidin, sodium ferrous gluconate, and calcium gluconate to control secondary hypocalcemia. Now requiring non-gynecological specialized care, the patient was transferred to the hospital's Department of Internal Medicine. The repeat laboratory tests taken in the unit appeared significantly improved; in particular, hyponatremia, hypochloremia and hypocalcemia had all regressed. Upon discharge, the patient was advised to continue treatment with hydrocortisone, combined with levothyroxine sodium to compensate for the hypopituitarism, and with folinic acid and iron gluconate to restore an adequate hematopoietic activity. The results of the patient's clinical examination and laboratory tests at three months' follow-up were satisfactory. The repeat MRI scan confirmed evidence of prior vascular necrosis.

## DISCUSSION

The Sheehan's syndrome, also known in the literature as postpartum pituitary necrosis, can be diagnosed from clinical and laboratory tests. The Sheehan's patient described in our case report presented with symptoms of asthenia, severe anemia and hyponatremia. Panhypopituitarism is often accompanied by normocytic normochromic anemia, which however is usually mild and seldom below 9g/dL values. The anemia that develops in the Sheehan's syndrome is due to cortisol deficiency, hypothyroidism and hypogonadism.

Our patient had severe anemia, which improved after adequate cortisone, thyroid hormone and iron treatment. While glucocorticoids stimulate erythropoiesis, thyroid hormones stimulate not only erythropoietin production, but also the proliferation of erythroid progenitor cells. The other noteworthy clinical finding in our patient was severe hyponatremia (though without neurological signs). Hyponatremia is a common electrolytic disorder, occurring in 33% to 69% of all cases with the Sheehan's syndrome. The causative factors of hyponatremia in our patient were volume depletion, cortisol deficiency and hypothyroidism. In Sheehan's patients, hyponatremia responds to combined NaCl, hydrocortisone and thyroxine treatment.

While early steroid treatment, associated with the administration of thyroid hormones and NaCl, is very important, the normalization of Na levels must be abrupt instead of gradual. At the doses used in our study, we were able to normalize Na levels without inducing any cerebral alterations, such as central pontine myelinolysis, which may otherwise occur when hyponatremia is not rapidly controlled.

Acute forms of the Sheehan's syndrome are rare and are usually diagnosed after e long time since delivery (up to 15–20 years). This delay is sometimes due to lack of symptoms or to their misrecognition. In the case reported here, the patient's asthenia prompted us to investigate for the presence of a pituitary deficit and, once the diagnosis was established, to start early treatment. In conclusion, our case report involves a rather rare form of Sheehan's syndrome, which was accompanied by severe anemia and hyponatremia that dramatically improved after adequate therapy with NaCl, thyroxine and hydrocortisone.

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## SUMMARY

Sheehan's syndrome is a well-known cause of panhypopituitarism secondary to pituitary apoplexy. Although the pathogenesis of the Sheehan's syndrome is not entirely clear, the primary causative factor is a widespread ischemic lesion of the pituitary gland resulting in the impairment of

anterior pituitary function. Here we present a case following spontaneous vaginal delivery that with a hormone therapy replacing and follow-up spontaneously resolved.

Opis przypadku zespołu Sheehana z ostrym początkiem, niedoborem sodu we krwi i ostrą anemią (niedokrwistością)

Zespół Sheehana jest dobrze znaną przyczyną panhipopituitaryzmu spowodowanego udarem przysadki. Jakkolwiek patogeneza zespołu Sheehana nie jest całkiem poznana, pierwotną przyczyną jest rozległy obszar niedokrwienia, powodujący zaburzenie funkcjonowania przedniego płata przysadki. W artykule przedstawiamy przypadek poporodowego zespołu Sheehana z hormonalną terapią zastępczą i samoistnym wyleczeniem.