CLINICAL CASE

Case report: severe hypoglycaemia as a late manifestation of Sheehan's syndrome

Caso clínico: hipoglucemia grave como manifestación tardía del síndrome de Sheehan

Edgar R. Romero-Vásquez[1], Luis A. Arteaga-Martínez[2], Germán Lachica-Rodríguez[2], and José Manuel Ornelas-Aguirre[3]*

[1]Internal Medicine Service, High Specialty Medical Unit, Mexican Social Security Institute (IMSS); [2]Internal Medicine Service, Regional General Hospital No. 1, IMSS; [3]Department of Health Sciences, University of Sonora. Ciudad Obregon, Sonora, Mexico

Abstract

Background: *Sheehan's syndrome is a hypopituitarism secondary to necrosis of the pituitary gland caused by massive postpartum bleeding. The presentation is frequently amenorrhea and agalactia; hypoglycemia as a solitary presentation is uncommon.* **Clinical case:** *68-year-old female with a history of postpartum hemorrhage 35 years ago. She had two episodes of hypoglycemia. During her hospital stay, panhypopituitarism was detected and the empty sella was confirmed by magnetic resonance imaging.* **Conclusions:** *It is recommended that medical personnel suspect Sheehan´s syndrome in any woman with nonspecific hypoglycemia and no history of chronic degenerative disease.*

Keywords: *Sheehan's syndrome. Hypoglycemia. Atypical presentation.*

Resumen

Antecedentes: *el síndrome de Sheehan es un hipopituitarismo secundario a necrosis de la glándula pituitaria causada por sangrado posparto masivo. La presentación es frecuentemente amenorrea y agalactia; la hipoglucemia como presentación única es poco común.* **Caso clínico:** *Mujer de 68 años con antecedente de hemorragia posparto hace 35 años. Tuvo dos episodios de hipoglucemia. Durante su estancia hospitalaria se detectó panhipopituitarismo y se confirmó la silla turca vacía mediante resonancia magnética.* **Conclusiones:** *Se recomienda al personal médico sospechar síndrome de Sheehan en toda mujer con hipoglucemia inespecífica y sin antecedentes de enfermedad crónico degenerativa.*

Palabras clave: *Síndrome de Sheehan. Hipoglucemia. Presentación atípica.*

Introduction

Sheehan's syndrome is a complication of postpartum hemorrhage[1], which was first described by the British pathologist H.L. Sheehan in 1937[2]. It appears as hypopituitarism secondary to necrosis of the pituitary gland caused by systemic arterial hypotension secondary to massive bleeding during labor[3]. Occurs in 1-2% of women[4] and its incidence in Mexico is 1/10,000 deliveries[5]. In Iceland, the prevalence is 5 cases per 100,000 women[6].

During pregnancy, hyperplasia of the pituitary gland develops, especially in the anterior region, in order to increase the production of prolactin necessary for lactation[6]. Irrigation of the pituitary gland predisposes to arterial ischemia during periods of arterial hypotension,

***Correspondence:**
Edgar R. Romero-Vásquez
E-mail: edgar_romerov22@hotmail.com

Date of reception: 30-08-2020
Date of acceptance: 27-10-2020
DOI: 10.24875/CIRUE.M20000314

Cir Cir (Eng). 2022;90(2):258-262
Contents available at PubMed
www.cirugiaycirujanos.com

since the superior pituitary artery enters the hypothalamus to form the portal system of capillaries, which courses through the stalk towards the anterior pituitary, whereby it is perfused with venous pressure[6]. The pituitary gland is formed by an anterior lobe that secretes prolactin, growth hormone, gonadotropins, adrenocorticotropin, and thyrotropin; the middle lobe secretes melanotropins, and the posterior lobe stores oxytocin and antidiuretic hormone secreted by the hypothalamus[7]. During childbirth, the presence of massive hemorrhage causes arterial hypotension, and consequently areas of necrosis can be generated[8].

Patients usually present months to years after the episode of postpartum hemorrhage[9], with an average time ranging from 2 to 33 years[10], due to incomplete pituitary damage and slow progression of damage[11]. In the late forms, the symptoms are variable depending on the hormonal deficit, with non-specific symptoms being frequent in more than 50% of women[11], followed by amenorrhea, sterility and hair loss due to gonadotropin deficiency, asthenia, fatigue, cold intolerance and premature aging due to thyroxine and growth hormone deficiency[4,11]. Patients may present with adrenal crisis due to cortisol deficiency or myxedema coma[11].

Clinical case

A 68-year-old woman with a history of postpartum hemorrhage at 33 years of age, with no clinical sequelae after said event (agalactia or amenorrhea). No family history of insulinoma. Diagnosed with major depressive disorder at the age of 38, under management with fluoxetine. In the interview she denied other chronic degenerative diseases. Her current condition began on April 12, 2019, when she went to a private hospital due to fatigue, adynamia, diaphoresis, weakness, confusion, and drowsiness; initial medical management included control of severe dehydration and hypoglycemia through parenteral glucose solutions, and she was discharged on the third day due to apparent general improvement. Twenty-five days after the onset of this condition, she presented the same symptoms again, but this time she was taken to the emergency department of our hospital. On admission, the patient presented a clinical picture characterized by severe hypoglycemia with weakness, dizziness, confusion, and drowsiness. Laboratory tests showed a serum glucose concentration of 30 mg/dl and normo-normo anemia (mean corpuscular volume [MCV] of 87 fl and mean corpuscular hemoglobin [MCH] of 31 pg). associated with hemoglobin of 9.0 g/dl, hematocrit of 24.4% and leukopenia of 3.9 × 10^9/l. A load of 50% glucose solution was administered parenterally, which resulted in almost immediate relief of symptoms, known as Whipple's triad (low blood glucose concentration, symptoms of hypoglycemia, and improvement once blood glucose normalized). She was admitted to the internal medicine service to continue with the hypoglycemia study protocol. Table 1 details the laboratory studies upon admission of the patient to the emergency department, in which severe hypoglycemia and anemia are evident. After admission to the internal medicine service, physical examination revealed skin depigmentation, mainly of the mammary areolas, mammary involution, and loss of axillary and pubic hair; no stigmata of chronic liver disease were found. Vital signs were normal. The presence of renal failure, chronic liver disease, and hypoglycemia secondary to medications or other substances, such as insulin, sulfonylureas, glinides, or alcohol, was ruled out based on the information and history obtained in the medical history. They inquired about some septic process or starvation that would explain the hypoglycemia, without success. For the evaluation of hypocortisolism and hyperinsulinism as the cause of hypoglycemia, serum cortisol and endogenous insulin were determined; with the results obtained, it was possible to determine the presence of hypocortisolism and decreased values of endogenous insulin, contrary to what could be expected in hyperinsulinemia. Table 2 shows the results of the laboratory studies performed during the

Table 1. Laboratory studies on admission of the patient to the emergency department, in which severe hypoglycemia and anemia are evident

Parameter	Value	Normal range
Glucose	↓ 30 mg/dl	60-100 mg/dl
Blood urea nitrogen	7 mg/dl	8-20 mg/dl
Urea	15 mg/dl	10-40 mg/dl
Hemoglobin	↓ 9.0 g/dl	14 ± 2 gr/dl
Hematocrit	↓ 24.4 (%)	42 ± 5 (%)
VCM	87 fl	80-97 fl
HCM	31 pg	27-31.2 pg
Leukocytes	↓ 3.9 ×10^9/l	4.5-11.5 ×10^9/l
Platelets	309,000 cel/mm^3	150,000-450,000 cel/mm^3

MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume.

Table 2. Laboratory studies during the patient's stay in the internal medicine service, in which hypopituitarism and hypoinsulinemia are evident

Parameter	Value	Normal range
Growth hormone	0.07 ng/ml	< 10 ng/ml
Somatomedin	↓ 3 ng/ml	17-241 ng/ml
Follicle stimulating hormone	↓ 0 mUI/ml	27-133 mUI/ml
Luteinizing hormone	↓ 0.1 mUI/ml	0.9-10.9 mUI/ml
Thyroid stimulating hormone	↓ 0.27 uU/ml	0.47-5.01 uU/ml
Morning serum cortisol	↓ 0,30 μg/dl	6.2-19.4 μg/dl
Free thyroxine	↓ 0.43 ng/dl	0.70-1,46 ng/dl
Endogenous insulin	↓ 1.0 uUI/ml	3.2-16.3 uUI/ml

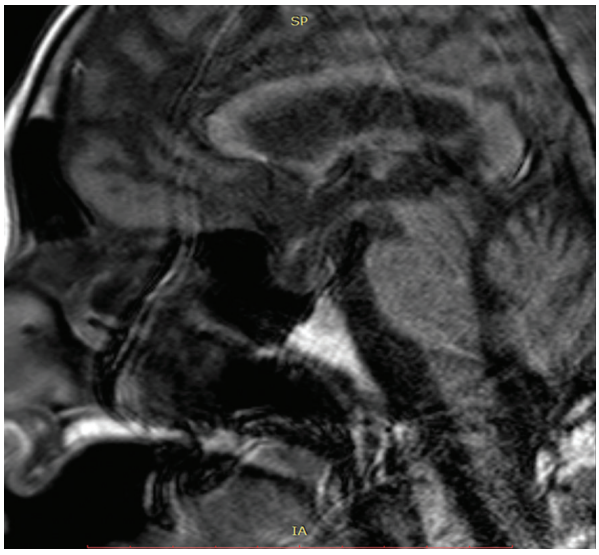

Figure 1. *Sagittal MRI of the skull in T1 sequence showing the presence of the empty sella turcica.*

patient's stay in the internal medicine department, in which hypopituitarism and hypothyroidism are evident. Abdominal computed tomography revealed no tumor masses in the pancreas or in the abdominal cavity, and therefore the hypothesis of an insulinoma as the cause of hypoglycemia was ruled out. Due to the low serum cortisol values, an MRI of the skull was performed in search of anatomical alterations, and the result was the presence of an empty sella turcica, therefore, with a history of postpartum hemorrhage, panhypopituitarism and the study of image was considered to be Sheehan's syndrome. Figure 1 shows the result of the magnetic resonance of the skull, which showed the empty sella turcica. Once the diagnosis was made, hormone replacement treatment was started. Prednisone was administered at a dose of 5 mg/24 h orally. This drug was chosen because it is the one available at our institution. The guidelines recommend the use of oral hydrocortisone as the first option for hormone replacement therapy[12-14], but in Mexico we do not have this preparation. Levothyroxine adjusted according to the patient's weight was administered at a dose of 1.6 μ g/kg of body weight every 24 hours (final dose of 100μg daily) to control hypothyroid symptoms and prevent complications such as myxedema coma. The improvement of the clinical picture was evident 14 days after starting the treatment.

Discussion

Pituitary gland failure occurs under various conditions: hypothalamic diseases such as craniopharyngiomas, metastasis of primary lung or breast tumors, secondary to central nervous system radiation, infections such as tuberculous and traumatic meningitis, and pituitary diseases such as adenomas or pituitary cysts. pituitary surgery, pituitary radiation, hemochromatosis, pituitary infection or abscess, and vascular causes such as stroke and Sheehan syndrome. Sheehan syndrome-related hypopituitarism is rare. Sheehan's syndrome is more common in developing countries[15]. Its diagnosis is based on a history of postpartum hemorrhage, lactation failure, deficiency of pituitary hormones, and the presence of a radiological image of an empty sella turcica in a cranial magnetic resonance study[16]. Our patient met all the criteria, but her atypical presentation occurred 35 years after the postpartum hemorrhage event and without lactation failure or amenorrhea. In recent years, several case series have been published on the late clinical presentation of Sheehan syndrome[17-22].

In a study conducted in India in 2016[18] Hormonal loss was reported in a group of 21 women diagnosed with Sheehan's syndrome, and it was found that the most frequent was for prolactin, gonadotropins and growth hormone[16-19,22-24], with clinical manifestation of insufficiency for lactation and amenorrhea. It is common to find that the drop in cortisol figures occurs in 50% of cases. Another study published in Xinjiang, China, in 2015, with 97 women with Sheehan syndrome, obtained similar results: the most frequent clinical presentation was loss of axillary or pubic hair in 85.6% of the cases studied, amenorrhea in 82.5%. and agalactia in 74.2%[24].

Other studies have suggested that the most common acute presentation is associated with adrenal crisis with cardiovascular collapse, hypoglycemia, hyponatremia, and shock[15,17]. The most frequent chronic presentation is with amenorrhea due to gonadotropin deficiency, agalactia, and breast involution, which can start even after several years of the postpartum hemorrhagic event with adrenal crisis or hypothyroidism, as happened in this case[7,15,22,23-27].

The main differential diagnosis is lymphocytic hypophysitis, which can occur in children and adults of both sexes, commonly associated with other autoimmune diseases, occurs without a history of postpartum hemorrhage, the most commonly affected hormones are the corticoid and thyroid axis, it is associated to hyperprolactinemia and diabetes insipidus, and in the magnetic resonance it is observed as a pituitary mass[11,27] Therefore, based on the patient's characteristics, clinical picture, and laboratory and imaging results, this diagnosis is unlikely.

The clinical presentation of our patient consisted of two episodes of hypoglycemia one month apart, which is an atypical presentation not reported in other studies. Hypoglycemia as part of an acute adrenal crisis is a relatively common clinical event, but in this case the patient did not present with adrenal crisis, but only isolated hypoglycemia. In a case series published by Ozkan and Colak[28] in 2005, the presence of hypoglycemia and hypothyroidism was found in 15% of the patients, which confirms the low prevalence of this clinical presentation. Kumar et al.[29] reported the case of recurrent hypoglycemia as a late presentation of Sheehan's syndrome. Another form of presentation reported is with episodes of hypoglycemia and hyponatremia[30].

In this case, once the diagnosis of Sheehan syndrome was made, her hormone replacement treatment was started, which produced clinical improvement and discharge from the hospital in a short time. Medical personnel need to be aware of this fact, since timely diagnosis and replacement therapy have a great impact on the morbidity and mortality of patients.

Acknowledgments

The authors thank Dr. Germán Lachica, Dr. Alberto Arteaga, and Dr. Manuel Ornelas for their support, time, and teaching.

Funding

The authors did not receive financing or support from any company outside the institute to carry out this article, everything was done by their own means and for academic purposes.

Conflicts of interest

The authors declare no conflicts of interest. Consent was obtained from the patient.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

References

1. Matsuzaki S, Endo M, Ueda Y, Mimura K, Kakigano A, Egawa-Takata T et al. A case of acute Sheehan's syndrome and literature review: a rare but life-threatening complication of postpartum hemorrhage. BMC Pregnancy Childbirth. 2017;17:188.
2. Dokmetas HS, Kilicli F, Korkmaz S, Yonem O. Characteristic features of 20 patients with Sheehan's syndrome. Gynecol Endocrinol. 2006;22:279-83.
3. Kelestimur F. Sheehan's syndrome. Pituitary. 2003;6:181-8.
4. Furnica RM, Gadisseux P, Fernandez C, Dechambre S, Maiter D, Oriot P. Early diagnosis of Sheehan's syndrome. Anaesth Crit Care Pain Med. 2015;34:61-3.
5. Casas Chávez CM, Mancera Castillo L, Muro Gaitán PB, Prieto Domínguez A, Campos Mendoza PE. Sheehan's syndrome. Description of a clinical case and review of the literature. Archives of Emergency Medicine of Mexico. 2013;5:38 AM-41.
6. Kilicli F, Dokmetas HS, Acibucu F. Sheehan's syndrome. Gynecol Endocrinol. 2013;29:292-5.
7. Ramos-López L, Pons-Canosa V, Juncal-Díaz J, Núñez-Centeno MB. Sheehan's syndrome after obstetric haemorrhage. Rev Esp Anestesiol Reanim. 2014;61:575-8.
8. Hale B, Habib AS. Sheehan syndrome: acute presentation with severe headache. Int J Obstet Anesth. 2014;23:383-6.
9. Laway B, Misgar R, Mir S, Wani A. Clinical, hormonal and radiological features of partial Sheehan's syndrome: an Indian experience. Arch Endocrinol Metab. 2016;60:125-9.
10. Contreras-Zúñiga E, Mosquera-Tapia X, Domínguez-Villegas MC, Parra-Zúñiga E. Sheehan syndrome: description of a clinical case and review of the literature. Rev Col Obstet Ginecol. 2009;60:377-81.
11. Karaca Z, Laway BA, Dokmetas HS, Atmaca H, Kelestimur F. Nat Rev Dis Primers. 2016;2:16092.
12. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:364-89.
13. Santini F, Pinchera A, Marsili A, Ceccarini G, Castagna MG, Valeriano R et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. J Clin Endocrinol Metab. 2005; 90:124-7.
14. Fish LH, Schwartz HL., Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. N Engl J Med 1987: 316(13):764.
15. Gokalp D, Alpagat G, Tuzcu A, Bahceci M, Tuzcu S, Yakut F et al. Four decades without diagnosis: Sheehan's syndrome, a retrospective analysis. Gynecol Endocrinol. 2016;32:904-7.

16. Shoib S, Dar MM, Arif T, Bashir H, Bhat M, Ahmed J. Sheehan's syndrome presenting as psychosis: a rare clinical presentation. Med J Islam Repub Iran. 2013;27:35-7.
17. Diri H, Tanriverdi F, Karaca Z, Senol S, Unluhizarci K, Durak AC, et al. Extensive investigation of 114 patients with Sheehan's syndrome: a continuing disorder. Eur J Endocrinol. 2014;171:311-8.
18. Laway BA, Mir SA, Gojwari T, Shah TR, Zargar AH. Selective preservation of anterior pituitary functions in patients with Sheehan's syndrome. Indian J Endocrinol Metab. 2011;15(Suppl 3):S238-41.
19. Sert M, Tetiker T, Kirim S, Kocak M. Clinical report of 28 patients with Sheehan's syndrome. Endocr J. 2003;50:297-301.
20. Dökmetaş HS, Kilicli F, Korkmaz S, Yonem O. Characteristic features of 20 patients with Sheehan's syndrome. Gynecol Endocrinol. 2006;22:279-83.
21. Gei-Guardia O, Soto-Herrera E, Gei-Brealey A, Chen-Ku CH. Sheehan syndrome in Costa Rica: clinical experience with 60 cases. Endocr Pract. 2011;17:337-44.
22. Diri H, Karaca Z, Tanriverdi F, Unluhizarci K, Kelestimur F. Sheehan's syndrome: new insights into an old disease. Endocrine. 2016;51:22-31.
23. Reddy MS, Nahar A, Thippeswamy H, Kumar CS. Psychosis as a late manifestation of Sheehan's syndrome. Asian J Psychiatr. 2017;25:228-30.
24. Du GL, Liu ZH, Chen M, Ma R, Jiang S, Shayiti M et al. Sheehan's syndrome in Xinjiang: clinical characteristics and laboratory evaluation of 97 patients. Hormones (Athens). 2015;14:660-7.
25. Shivaprasad C. Sheehan's syndrome: newer advances. Indian J Endocrinol Metab. 2011;15 (Suppl3):S203-7.
26. Reddy MS, Nahar A, Thippeswamy H, Kumar CS. Psychosis as a late manifestation of Sheehan's syndrome. Asian J Psychiatr. 2017;25: 228-30.
27. Shoib S, Dar MM, Arif T, Bashir H, Bhat MH, Ahmed J. Sheehan's syndrome presenting as psychosis: a rare clinical presentation. Med J Islam Repub Iran. 2013;27:35-7.
28. Ozkan Y, Colak R. Sheehan's syndrome: clinical and laboratory evaluation of 20 cases. Neuro Endocrinol Lett. 2005;26:257-60.
29. Kumar N, Singh P, Kumar J, Kumar Dhanwal D. Recurrent hypoglycemia: a delayed presentation of Sheehan syndrome. BMJ Case Rep. 2014;2014:bcr2013200991.
30. Jose M, Amir S, Desai R. Chronic Sheehan's Syndrome – a differential to be considered in clinical practice in women with history of postpartum hemorrhage. Cureus. 2019;11:e6290.