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Acute Sheehan's Syndrome Presenting with Diabetes Insipidus: A Rare Case Report

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Abstract: *Sheehan's syndrome, or postpartum pituitary necrosis, is a rare disorder with a complex and often delayed diagnosis. The initial damage is caused by massive postpartum hemorrhage (PPH) resulting in insufficient blood flow to the pituitary gland. Symptoms usually appear years after delivery but may become acute in rare cases. The most common and earliest hormone deficiency is GH deficiency, followed by other hormone deficiencies. Dysfunction of the posterior pituitary gland is more rare disorder responsible for the onset of diabetes insipidus secondary to antidiuretic hormone (ADH) deficiency. The authors report the case of a patient who presented clinically favorable to acute Sheehan syndrome 25 days after postpartum hemorrhage, with extreme weakness, incoercible vomiting, weight loss, amenorrhea, lack of lactation, polyuria, and polydipsia. Biological tests showed electrolyte disorders such as hyponatremia and hormonal deficits. Pituitary magnetic resonance imaging (MRI scan) showed an empty sella turcica aspect. The diagnosis of acute Sheehan syndrome with posterior pituitary and anterior pituitary insufficiency was retained. This case report describes the clinical, biological, and radiological characteristics of acute Sheehan syndrome and discusses the possibility of its early diagnosis and its first symptoms. Furthermore, it demonstrates the long-term efficacy of hormonal replacement as the only management option available and the importance of reducing postpartum hemorrhage as the best prevention method.*

INTRODUCTION:

The pituitary is a gland located in the sella turcica and consists of 2 lobes the anterior lobe (adenohypophysis) responsible for the secretion of Growth hormone (GH), Prolactin (PRL), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Thyroid-stimulating hormone (TSH) and Adrenocorticotropic hormone (ACTH). Its damage is responsible for the disruption of several endocrine axes. The posterior lobe (neurohypophysis) is responsible for the secretion of antidiuretic hormone (ADH) and oxytocin, its damage causes diabetes insipidus. Damage of the pituitary gland in Sheehan's syndrome can involve one lobe or both lobes [1]. Pituitary insufficiency can be caused by a variety of pathological processes, including tumors, infections, granulomas, metabolic, autoimmune diseases, and surgical or radiation interventions [2]. Postpartum pituitary necrosis or Sheehan's syndrome was one of the first described disorders associated with pituitary insufficiency. Improving the quality of obstetric care through the use of uterotonics has reduced the incidence of Sheehan's syndrome, but postpartum pituitary necrosis remains a major problem in underdeveloped countries [3]. This report describes a case of acute onset pituitary insufficiency involving the anterior lobe as well as the posterior lobe of the pituitary gland with the onset of diabetic insipidus which makes it rare, and through a review of the literature, it provides insight into the time of onset of Sheehan's syndrome, the prevalence of acute onset, its clinical, biological, and radiological characteristics, to show the importance of managing postpartum hemorrhage in preventing disease and providing news about treatment.

CASE PRESENTATION:

Mrs. S.Z, 37 years old, 3rd gesture and 3rd parity. She was admitted to the emergency department for profound asthenia, incoercible vomiting and lack of lactation that occurred 25 days after delivery complicated by severe postpartum hemorrhage that required a total hysterectomy for maternal rescue, massive transfusion with red blood cells and platelets and fresh frozen plasma, and a 10 day stay in the intensive care unit where the patient was intubated and ventilated for multi-visceral failure after hemorrhagic shock.

Physical examination on admission showed a conscious patient, well oriented in time and space with polyuria more than 3.5 l/day made of less concentrated urine, weight loss of 7 kg in 25 days, pallor and doughy skin and her breast tissue was normal but the areolae were depigmented. As for the lab results, the initial lab test showed hyponatremia at 119 mmol/L, her hemoglobin level was 8.1 g/dL, her leukocyte count was 3×10^9/L with a neutrophil count of 1.8×10^9/L, her platelet count was at 155×10^9/L. Based on

a hormonal assessment ordered, Free thyroxine was low at 2.3 pmol/L with an inadequate level of thyroid-stimulating hormone 2 µU/L, Her basal serum cortisol (measured at 8 a.m.) was 140 nmol/L and her prolactin level was 2 ng/ml. An osmolarity test on the urine showed a low level of 18 mOsm/kg. She was clinically and biologically diagnosed with Sheehan's Syndrome. The Patient underwent a Magnetic Resonance Imaging scan (MRI scan) of the pituitary gland (figure 1) revealed a normal sella turcica. She was symptomatic even though the radiological appearance was normal.

The dehydration was corrected by filling. Hypothyroidism was corrected by progressive replacement with L-thyroxine at 24µg/week until symptoms related to hypothyroidism were corrected, clinical euthyroidism was achieved at a dose of 100 µg/day. Glucocorticoid treatment was initiated immediately after biological confirmation of adrenal insufficiency with a progressive increase in dose until reaching 20mg/day of hydrocortisone. In order to replace Antidiuretic hormone (ADH), the patient was treated with desmopressin at a dose of 0.2 mg/day. Our patient was under intensive observation for nine weeks after discharge from the hospital, during this period the clinical symptomatology gradually improved and complete hematological recovery was noted, with eucortisol and euthyroid status, elevated hemoglobin level was noted and replacement therapy was prescribed for life.

Six months after the diagnosis of Sheehan's syndrome, the patient was referred to the radiology department for MRI scan for progression of the radiographic aspects of pituitary necrosis. The MRI showed a completely empty sella turcica filled with cerebrospinal fluid. (figure 2) the patient was always asymptomatic on hormone replacement therapy (HRT) and hormonal test was ordered once every 6 months.

The time between the hemorrhagic event and the diagnosis of Sheehan's syndrome varies from a few weeks to several years and is often delayed [4]. In our case, the time to diagnosis is 25 days which is considered early or acute. To discuss the time from diagnosis to the onset of bleeding, we chose the cohort conducted by Sert et al., which set a mean time to diagnosis of 13.9±6.0 years (n=28) [5]. This finding shows a long delay in the diagnosis of Sheehan's syndrome, consistent with the study of Gei-Guardia et al. [6] (n=60) with a delay of 13 years and 9±9.7 years in that of Ramiandrasoa et al. [7] (n=39). Long delays in diagnosis can be seen in these cohorts, which may have several causes. First, we can observe different degrees of hypopituitarism, which give rise to different signs. Most women with Sheehan's syndrome are asymptomatic until a stressful event occurs and triggers adrenal insufficiency or hypothyroidism, which is another reason to explain the delayed diagnosis [8]. Furthermore, patients with ACTH deficiency still produce more aldosterone than do patients with peripheral adrenal insufficiency, whose clinical signs are typically more severe. Another hypothesis to explain the long delay in the diagnosis is that most signs of Sheehan's syndrome are aspecific, particularly during the postpartum period. Indeed, most women experience asthenia and weakness after childbirth and can be misdiagnosed as having baby blues or depression [7]. However, due to the rarity of Sheehan's syndrome, it is impossible to perform an anterior pituitary test for all tired postpartum women. An additional reason for misdiagnosis is that SS is so rare and unwonted among doctors and midwives, which can explain the long delay of diagnosis.

Early diagnosis of acute Sheehan's syndrome is often very difficult and is rarely considered in the first month after a bleeding event. The first symptoms that can orient us are those considered banal and non-specific, namely the lack of lactation and amenorrhea, and the latter may be physiological symptoms after childbirth, which delay the diagnosis [9,10]. In our case, the patient displayed both symptoms, but endocrine signs caught our attention. The clinical manifestations of Sheehan's syndrome vary from one patient to another. As with hypopituitarism of other origins, hormone deficiency ranges from the loss of a single hormonal axis to complete hypopituitarism. In one of the largest series examining endocrine function, 86% of patients had panhypopituitarism and 14% had selective hypopituitarism [11]. In another study, 56.2% of patients had panhypopituitarism and 43.8% had selective hypopituitarism [12]. GH and PRL are the most commonly affected hormones. PRL deficiency leads to postpartum lactation failure, and gonadotropin (FSH and LH) deficiency leads to amenorrhea and regression of secondary sexual characteristics. Extensive pituitary necrosis can also lead to TSH and less commonly ACTH deficiency, which can lead to symptoms related to hypothyroidism such as constipation, depression, and cold intolerance, followed by symptoms related to adrenal insufficiency such as weakness, weight loss, hypotension, and hypoglycemia. The acute insufficiency of the posterior pituitary (neurohypophysis) may be present and responsible for ADH deficiency which manifests itself as polyuria and polydipsia. Loss of water and electrolytes at the renal level may be responsible for extracellular and intracellular dehydration and hydroelectrolytic imbalance that may be severe. The fact that the neurohypophysis is less frequently involved than the anterior Pituitary (adenohypophysis) suggests that the anastomotic arterial ring around the infundibular process is protective for the neurohypophysis, while the adenohypophysis has two different blood supplies. Neither the superior pituitary artery nor the portal system has anastomotic vascularization, the latter has a lower oxygen concentration because it is the portal system [13]. Therefore complete necrosis of the pituitary gland can lead to serious clinical consequences such as circulatory collapse, myxedema, hyponatremia, coma and death if not treated properly. The death rate in patients with Sheehan's syndrome is 1.2 to 2.7 times higher than in the general population [14].

Some patients are diagnosed with symptoms of acute hypopituitarism immediately after delivery. Diagnosis of acute Sheehan's syndrome is difficult due to the combination of symptoms associated with hemorrhagic shock and its complications [15]. Few studies

focused on early Sheehan's syndrome, we found only one literature review on the topic, involving 53 articles, we identified 21 eligible reports, and added our case [16]. Table 1 summarizes the 22 cases. We chose the issue of characterizing acute Sheehan's syndrome for further discussion. Of the identified cases, 17 described the extent of postpartum hemorrhage, major hemorrhage, or even shock in 16 patients, however, in one case, approximately 500 ml of postpartum hemorrhage (PPH) induced an acute Sheehan's syndrome. These results indicate that most cases of acute Sheehan's syndrome occur after the postpartum hemorrhage, consistent with its pathophysiology. The first signs appeared in 17 of 22 patients within 10 days after delivery. Therefore, during this period, obstetricians should pay special attention to early signs of the syndrome. The first complications were hyponatremia due to adrenal insufficiency in 13 cases, diabetes insipidus in 5 cases, and the hypothyroidism in 2 cases. Panhypopituitarism or complete pituitary insufficiency was observed in 4 cases. It is important to keep in mind that the time between the first signs and delivery varies depending on the type of complication. For posterior hypopituitarism, the median time to onset of diabetes insipidus was 4 days (1-7 days), for anterior pituitary insufficiency, it was 7.9 days (14-19 days) for adrenal insufficiency, 18 days (16-20 days) for hypothyroidism and for panhypopituitarism was 9 days (4-17 days). In our review of the literature, 6 of 22 patients reported severe headache on the day of delivery. The causes of postpartum headaches vary and they can be difficult to diagnose accurately. The presence of severe headaches may indicate Sheehan's syndrome, but only after serious brain lesions have been ruled out.

For laboratory findings, some studies have been selected and categorized to analyze endocrine abnormalities and biological significance associated with Sheehane's syndrome[1,6,7,11,17]. Table 2 summarizes outcome statistics for different endocrine abnormalities results. One possible reason for the discrepancy between studies is the time from the onset of signs to diagnosis. Through the table, we note that the most common and precocious hormonal impairment was GH deficiency, followed by deficiency in other hormonal axes in an almost similar way. Partial impairments progressed to complete impairment over time, which explains the severity of the disease [18]. As for the posterior pituitary, its damage is rare and can be responsible for central diabetes insipidus.

With regard to radiological findings, Pituitary magnetic resonance imaging (MRI) is the radiological examination of choice if Sheehan's syndrome is suspected, and has a high sensitivity to pituitary involvement. Ozkan et al. studied 20 patients with a clinical and biological suspicion of Sheehan's syndrome, MRI scan results were in favor of sella turcica damage in 100% of cases (11 patients had empty sella and 9 patients had partial empty sella)[19]. MRI findings vary according to the stage of disease and severity of involvement, which may have aspects in the acute phase, such as nonhemorrhagic enlarged pituitary gland with central infarction [15, 18]. After weeks to months, the gland can shrink to the limit of the sella turcica, followed by progressive atrophy over the years [3,4]. Regarding the severity of the damage, the sella turcica may be partially (25–30%) or completely (70–75%) empty at the time of imaging [7,18]. It should be added that there is no correlation between the extent of pituitary necrosis and the severity of clinical manifestations, as well as between the degree of hypopituitarism and the emptiness of the sella turcica on MRI scan which can be explained by the inoperability of the remaining tissue in the partially empty sella [18].

Prevention of Sheehan's syndrome relies primarily on prevention, correction, and effective management of postpartum hemorrhage[1]. It is considered the leading cause of maternal mortality worldwide, especially in developing countries[20]. A study of 275,000 births in several developing countries found that 1.2% of deliveries were associated with postpartum hemorrhage. Among women with postpartum hemorrhage, 18% had adverse maternal outcomes and 3% died. There is a shortage of medical personnel in these countries. Although they account for 25% of the global burden of obstetric disease, only 1.3% have qualified healthcare providers, including doctors, nurses, and midwives[21]. To prevent PPH-related morbidity and mortality, these risk factors must first be corrected. Maternal anemia is one of the most important preventable risk factors; it is prevalent in developing countries and can be prevented by iron supplementation when iron deficiency occurs. There are other risk factors that are less preventable such as previous cesarean section, low-lying placenta, high fetal weight, long labor, and others[22]. To prevent complications associated with postpartum hemorrhage, the World Health Organization (WHO) has published important treatment guidelines and protocols, including a well-coded set of interventions to organize management. These protocols contain practical tips, such as the use of uterotonic agents, management techniques, and classifications of management, with the goal of establishing effective and versatile management[21]. The treatment of postpartum hemorrhage (PPH) has also been improved by the use of prostaglandins as potent[23].

Management of Sheehan's syndrome depends on treating the hypopituitarism. It should also be noted that hormone replacement therapy does not improve pituitary function or prevent the development of pituitary necrosis, but rather replaces its function which requires regular monitoring as hypopituitarism progresses[18]. Glucocorticoid therapy should begin immediately after obtaining serum samples to measure cortisol and ACTH levels in patients with acute exacerbations with a high clinical suspicion of adrenal insufficiency[24]. The dose of glucocorticoids should be adjusted based on the patient's clinical presentation rather than laboratory findings. Secondary adrenal insufficiency requires lifelong glucocorticoid therapy. With regard to thyroid hormone replacement, dose titration of levothyroxine is based on levels of thyroxine (T4) and free triiodothyronine (T3) and not on levels of TSH, which can be normal, low, or elevated[25]. There are a variety of formulations of levothyroxine, such as tablets, soft oral capsules, and liquid formulations. Although estrogen-progesterone replacement therapy for postmenopausal women with Sheehan's syndrome is controversial. For young women, higher doses of estrogen are preferred, while lower doses are used once menopause begins, and it

is recommended to discontinue treatment in women over the age of 50 [24]. Opinions on the effectiveness and routine use of GH therapy for patients with Sheehan's syndrome have been divided according to the benefit/risk balance [24]. In a study involving 91 patients from 19 countries, 1-year GH replacement therapy improved quality of life, body composition, and lipid profile [25]. Moreover, for patients with severe GH deficiency, replacement therapy improves sympathetic tone. In contrast, some parameters were not improved with GH replacement therapy. In this latest study, Tanriverdi et al. [26] showed that 6 months of GH replacement therapy failed to improve abnormal sleep patterns in Sheehan's syndrome patients who displayed more non-rapid eye movement (NREM).

Diabetes insipidus may be due to damage to the posterior pituitary gland, which results in impaired secretion of antidiuretic hormone [24]. Desmopressin is a modified form of ADH that can be administered orally, nasally, or parenterally, usually at bedtime, but morning and afternoon doses can be added if an increased anti-diuretic effect is desired. When given nasally, the antidiuretic effect of desmopressin occurs within 6 to 12 hours. However, when given orally, the duration of action is shorter.

CONCLUSION:

Most people with Sheehan's syndrome have non-specific symptoms, such as weakness, cold intolerance, anemia, and malaise, which can affect quality of life, especially because of the long delay in diagnosis[3]. These patients may go undiagnosed or misdiagnosed for long periods of time and receive inadequate treatment. In addition, hormonal deficiencies develop and worsen over time, indicating a gradual exacerbation of this chronic disease. Undiagnosed Sheehan's syndrome is associated with increased mortality and morbidity, although no prospective studies have specifically addressed the morbidity and mortality of Sheehan's syndrome. Greater understanding of the disease will lead to earlier diagnosis and treatment, improving quality of life and reducing morbidity and mortality.

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COMPETING INTERESTS :

Authors have declared that no competing interests exist.

FIGURES :

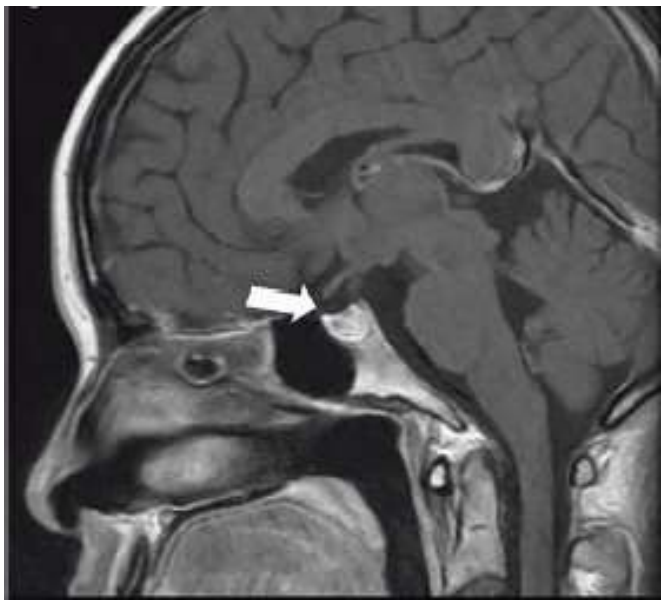

Figure 1: Radiological features of Sheehan's syndrome in the acute phase. | Postcontrast MRI of the pituitary gland 30 days after postpartum hemorrhage shows a normal-looking sella turcica on T1-weighted images.

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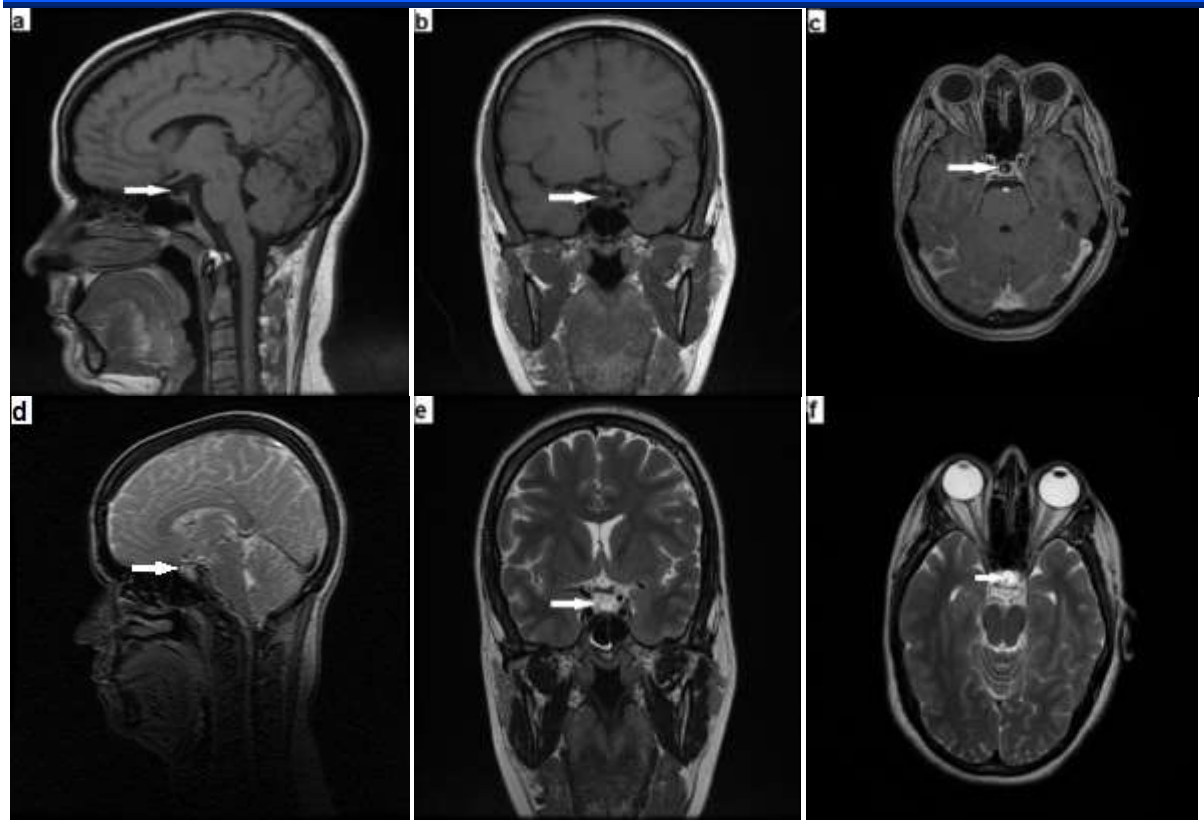

Figure 2: Radiological features of Sheehan's syndrome in the chronic phase. | Postcontrast MRI of the pituitary gland 6 months after postpartum hemorrhage showing empty sella turcica on T1-weighted images (a,b,c) and hyperintensity (sella turcica filled with cerebrospinal fluid) on T2-weighted images (d,e,f). | Sagittal (a,d), coronal (b,e) and transverse (c,f) sections. | The size of the sella turcica is normal.

TABLES :

Table 1: a summary of the literature review findings for acute Sheehan's syndrome[16]

	diagnosis time				**Blood loss**			**Shock**		
	less than one day	between one day and one week	between 1 and 2 weeks	between 2 weeks and one month	low abundance	great abundance	not described	presented	Not presented	not described
number of cases	2	9	6	5	3	14	5	14	4	4

	Symptoms					**Causes**				
	headache	failure to lactate	asthenia	vomitting	convulsions	hyponatremia	adrenal insufficiency	diabetes insipidus	hypothyroidism	panhypopituitarism
number of cases	7	3	6	2	2	10	11	5	2	3

Table 2: Anterior pituitary hormone deficiency in Sheehan's syndrome [1,6,7,11,17]

Study	*n*	GH deficiency (%)	PRL deficiency (%)	FSH and LH deficiency (%)	TSH deficiency (%)	ACTH deficiency (%)
Karaca et al. [1]	495	99	84	77	84	80
Zargar et al. [17]	149	60	85	80	58	54
Haddock et al. [11]	50	98	86	94	88	96
Gei-Guardia et al. [6]	38	100	100	75	80	97
Ramiandrasoa et al.[7]	27	96	57	80	92	83

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; n, number of cases.

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