Review

Sheehan's syndrome

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Summary

Sheehan's syndrome is postpartum hypopituitarism resulting from pituitary necrosis due to severe hypotension or shock secondary to massive bleeding during or following delivery. Sheehan's syndrome is one of the neglected endocrine disorders. Although the definite mechanisms have not been clearly defined; disturbed blood supply of the pituitary gland due to hypotension in addition to increased demand of the gland due to physiological enlargement during gestation, relatively small sella size and autoimmunity in the longterm are suggested factors that are involved in the pathogenesis. Sheehan's syndrome is characterized by variable degrees of hypopituitarism. Patients may have isolated, partial or complete hypopituitarism and they present with symptoms or signs due to the deficient hormone(s). The main difference from hypopituitarism due to other causes, such as pituitary adenoma or pituitary surgery, is the severity of the hormonal insufficiency. The symptoms and signs depend on the type and the severity of the underlying hormonal insufficiency. A history of failure of postpartum lactation and resumption of normal menses are the most common diagnostic features suggesting Sheehan's syndrome. Partial or complete empty sella on MRI or CT is almost always seen in the patients. Treatment includes appropriate replacement of deficient hormones.

KEY WORDS: postpartum hypopituitarism; Sheehan's syndrome; empty sella.

Introduction

Sheehan's syndrome refers to postpartum hypopituitarism resulting from pituitary necrosis due to severe hypotension or shock secondary to massive bleeding during or following delivery. Sheehan's syndrome is one of the neglected endocrine disorders. It was first described by HL Sheehan in 1937 (1). Because of its rarity in Western Society, it has become a forgotten disorder supposed to be seen only in underdeveloped countries in which obstetrical care is not adequate and treatment options to prevent the development of the syndrome are not available. Nowadays, doctors including endocrinologists are not given sufficient information regarding Sheehan's syndrome during their medical education, so they are not aware of its clinical presentation. For this reason, most patients with Sheehan's syndrome are unrecognized and thereby untreated for a long time until admitted to the emergency departments in a poor condition due to the complication of severe hypopituitarism. During the last decades social and economical problems have caused a huge amount of immigration from underdeveloped and poor countries to more developed and richer countries. Patients with subtle hypopituitarism due to Sheehan's syndrome among immigrants are not correctly diagnosed because medical staff are unaware of the syndrome. Some of these patients are diagnosed by immigrant doctors who have seen patients with similar symptoms previously in their homeland. So, obviously, the prevalence of Sheehan's syndrome in Western Society is underestimated. Supporting this idea, recent data from a European study in which 1034 patients were enrolled in the KIMS-Pfizer International Metabolic Database the majority of whom were European in origin, showed that the prevalence of Sheehan's syndrome was 3.1%, making it the sixth most common cause of adult GH deficiency (2). Another study from Iceland, a European country in which the obstetrical care is undoubtedly modern, showed a prevalence of 5.5 per 100, 000 in the Icelandic population (3). The highest prevalence of Sheehan's syndrome nowadays is reported in India; in one study it was calculated that the projected number of women with Sheehan's syndrome among a total population of parous females aged ≥ 20 years (12, 32, 827) would be 38, 691 in the Kashmir valley (4). In a very recent study from France, 39 patients with Sheehan's syndrome were reported and they experienced a long diagnostic delay (5).
Sheehan's syndrome is probably the most common cause of hypopituitarism in underdeveloped countries. In some developing countries, including Turkey, the presence of Sheehan's syndrome is still due to relatively late diagnosis in patients who had peri or postpar-

tum bleeding leading to pituitary necrosis a long-time ago; for example 20-30 years ago. Another important factor revealing unrecognized cases is the increasing number of experienced medical staff who are familiar with Sheehan's syndrome.

Clinical Picture

Sheehan's syndrome is characterized by variable degrees of hypopituitarism. Patients may have isolated, partial or complete hypopituitarism and they present with symptoms or signs due to the deficient hormone (s). The main difference from hypopituitarism due to other causes, such as pituitary adenoma or pituitary surgery, is the severity of the hormonal insufficiency. For example GH deficiency is more severe in Sheehan's syndrome patients than in patients with non-functional pituitary adenoma (6). The frequency of panhypopituitarism was reported as 55-86% and GH deficiency was diagnosed almost always in all patients with Sheehan's syndrome (6-8). The diagnosis of Sheehan's syndrome is usually made in patients months to years later. The symptoms and signs depend on the type and the severity of the underlying hormonal insufficiency. A history of failure of postpartum lactation and resumption of normal menses are the most common diagnostic features suggesting Sheehan's syndrome. We proposed the following criteria for the diagnosis of Sheehan's syndrome: 1-Typical obstetrical history of severe postpartum vaginal bleeding, 2-Severe hypotension or shock which requires blood transfusion or fluid replacement, 3-Failure of postpartum lactation, 4-Failure to resume regular menses after delivery, 5-Varying degrees of anterior pituitary failure, 6-Empty sella on CT scan or MRI (9). Most patients may have subtle hypopituitarism characterized by nonspecific manifestations including fatigue, weakness, mild hypotension, cold intolerance and feeling unwell. These patients may remain undiagnosed or misdiagnosed for a long time and receive inappropriate treatments such as vitamin supplementation and antidepressive agents. Therefore, the clinical presentation in the majority of patients with Sheehan's syndrome is subclinical and at least some of them are seen for the first time in emergency departments in a hypoglycemic and/or hypocortisolemic state after they have been subjected to a stressful condition such as an infection which may result in coma and death. Sheehan's syndrome accounted for 8% of 126 patients hospitalized because of hypoglycemia in one university hospital. It was the 7th most common cause of hypoglycemia (10). The signs and symptoms of Sheehan's syndrome are shown in Table 1. Hypothyroidism in Sheehan's syndrome is usually less severe than primary hypothyroidism and some findings such as facial edema and periorbital puffiness are not present in Sheehan's syndrome patients. Hypopigmentation instead of hyperpigmentation may be seen in patients with Sheehan's syndrome. Fine wrinkling around the eyes and mouth presumably due to long-term GH and estrogen deficiencies create the typical appearance of a patient with Sheehan's syndrome. Differential diagnosis of Sheehan's syndrome should include spontaneous infarction of a pituitary adenoma due to hypotension during or after delivery in which decompressive surgery may be necessary, autoimmune hypophysitis which may result in empty sella as a final outcome and primary empty sella syndrome (11,12).

Table 1 - The manifestations of Sheehan' syndrome.

1.	Agalactia
2.	Amenorrhea
3.	Infertility
4.	Hypotension
5.	Psychiatric disorders
6.	Intolerance to fasting/hypoglycaema
7.	Weakness
8.	Tiredness
9.	Breast atrophy
10.	Fine wrinkling on the face
11.	Loss of hair
12.	Cold intolerance
13.	Empty sella (partial or complete) on MRI
14.	Cognitive dysfunction
15.	Sleep disorders (more non REM and less REM sleep)
16.	Skin abnormalities (decreased sebum content and skin hydration)

Pathogenesis

Although the definite mechanisms responsible for the development of postpartum pituitary necrosis have not been clearly defined, recent data have given new insight into the pathogenesis. The pituitary gland is physiologically enlarged during pregnancy (13). Blood supply may be compressed because of an enlarged pituitary gland and decreased sella size which has been reported in most of patients with Sheehan's syndrome (9,12,14). Blood flow to the pituitary may be comprimised due to vasospasm following untreated severe hypotension associated with hemorrhage. All these factors make the pituitary more susceptible to ischemia in a pregnant woman (9,12,15). Pituitary dysfunction in Sheehan's syndrome may worsen over the years. For this reason the clinical picture is generally worse when Sheehan's syndrome is diagnosed. One of the anterior pituitary hormones which is normal at the beginning may be lost during the course of the syndrome. Therefore, it would be expected that an autoimmune process may be involved in the worsening of pituitary dysfunction. Some studies suggest that antipituitary antibodies (APAs) may be detected in the circulation of patients with Sheehan's syndrome (16-18). On the other hand, Goswami et al. reported that sequestered antigens due to tissue necrosis which could trigger autoimmunity may be responsible for the delayed hypopituitarism seen in Sheehan's syndrome (17). In order to understand

whether an autoimmune process can contribute to late hypopituitarism, we evaluated the presence of antihypothalamic antibodies (AHAs) and APAs in 20 women with Sheehan's syndrome and found AHA positivity in 40% and APA positivity in 35% of the patients. These results clearly suggest that an autoimmune process involving both the hypothalamus and pituitary gland may contribute to late pituitary dysfunction in Sheehan's syndrome (19). On the other hand, Atmaca et al. reported that Sheehan's syndrome is characterized by a marked variation in some peripheral lymphocytes cell subsets indicating altered immune regulation (20). Prothrombin time and INR are increased in Sheehan's patients when compared to normal women which might suggest that coagulation abnormalities may be one of the predisposing factors of postpartum hemorrhage (21-23). The pathogenesis of Sheehan's syndrome is shown in Figure 1.

Posterior pituitary functions

Previous autopsy studies showed that in over 90% of patients with Sheehan's syndrome the posterior lobe of the pituitary gland and hypothalamic nuclei were atrophic (24,25). Posterior pituitary functions have not been extensively investigated in patients with Sheehan's syndrome. Another reason for the lack of data regarding posterior pituitary function is that only a few patients with Sheehan's syndrome may present with overt diabetes insipidus (26-28). We and others have reported that there are subtle defects in posterior pituitary functions and partial diabetes insipidus is more common than expected (29,30). We have also found that the threshold for thirst perception was increased in Sheehan's syndrome patients and plasma osmolalities at baseline and after hypertonic saline infusion were significantly higher in patients than in control women. On the other hand, GH replacement therapy for 3 months did not reverse the mildly deteriorated posterior pituitary functions (31). Hyponatremia is not uncommon and the main causes are untreated adrenal failure and inappropriate vasopressin secretion (Tab. 2).

Table 2 - Water and electrolyte disturbances in Sheehan's syndrome.

1.	Central diabetes insipidus
2.	Partial diabetes insipidus
3.	Increased threshold for thirst perception
4.	Hyponatremia

Laboratory Investigation

In the investigation of anterior pituitary function in patients suspected with Sheehan's syndrome the first step is the measurement of basal hormone levels which may be sufficient to diagnose Sheehan's syndrome in some patients who have typical obstetrical history. Ho-

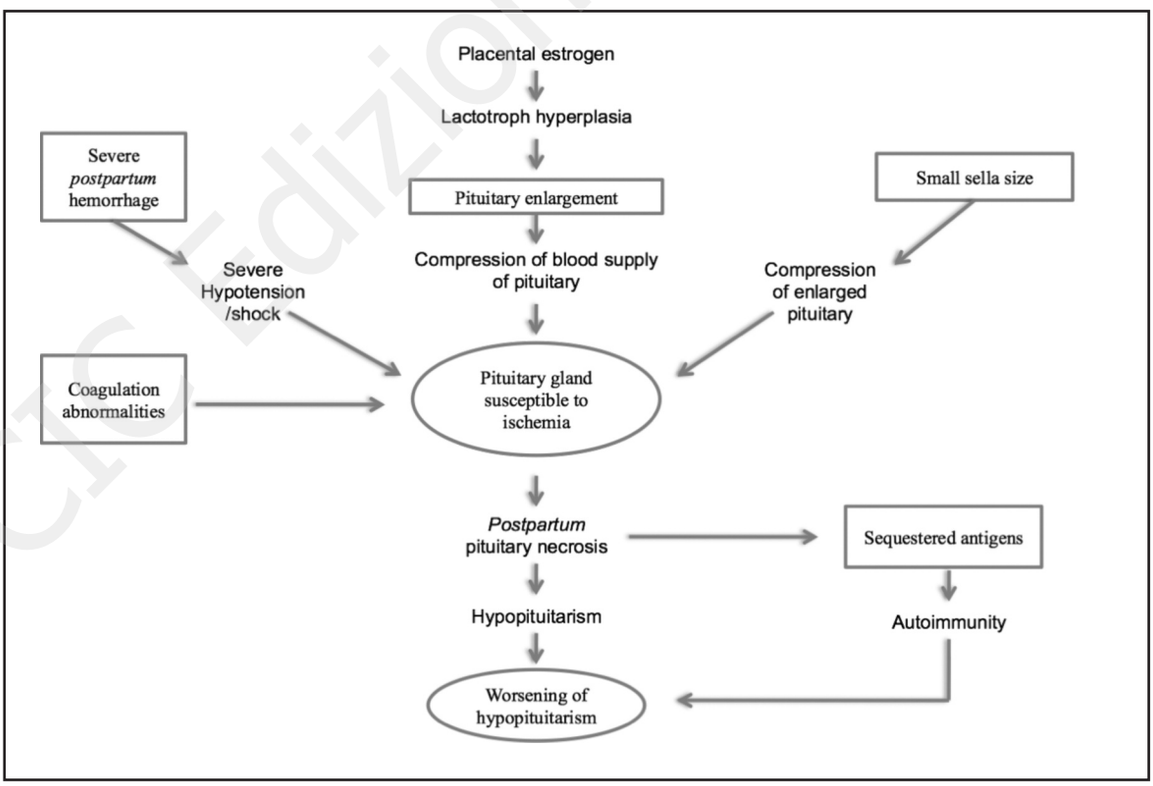

Figure 1. Pathogenesis of Sheehan's syndrome.

wever most patients may require dynamic pituitary function tests including insulin tolerance test, ACTH stimulation test, glucagon stimulation test, a GHRH-arginine stimulation test because a diagnosis of subclinical hypopituitarism may not be possible with basal hormone measurement alone. Currently the TRH stimulation test used to diagnose central hypothyroidism and hypoprolactinemia has ceased to be used since very sensitive TSH assays have become commonly available. However it was shown that when both free T3 and TSH levels were in the low-normal ranges the TRH stimulation test may be helpful in the diagnosis (32).
Partial or complete empty sella on MRI or CT is almost always seen in all patients with Sheehan's syndrome. MRI is the preferred radiological procedure for imaging of the hypothalamo-pituitary region in Sheehan's syndrome patients.

Treatment

Treatment of a patient with Sheehan's syndrome is not different from that of a patient with hypopituitarism due to other causes. Deficient hormones should be replaced appropriately. Thyroid hormone and glucocorticoid replacement therapy is crucially important if they are deficient. Replacement therapy including estrogen and progesterone depends on the menopausal status of the patient; premenopausal women with Sheehan's syndrome require estrogen and progesterone replacement therapy unless there is a contraindication. Estrogen and progesterone replacement therapy in hypogonadal postmenopausal women with Sheehan's syndrome is controversial but the current data are not in favor of this treatment because of the side effects, including thromboembolic events in particular. One of the most controversial issues regarding replacement therapy is related to GH replacement therapy (GHRT). We have extensively investigated the effects of GHRT on different parameters in patients with Sheehan's syndrome (33). Only severely GH deficient patients are suitable candidates for GHRT. We have reported that GHRT has beneficial effects on cognitive functions as detected by the latency of P300 auditory potentials (34).
It was shown that GH replacement therapy has beneficial effects on Quality of Life, body composition and the lipid profile (6). GHRT for 6 months is not sufficient to improve disturbed sleep architecture due to severe GH deficiency in Sheehan's syndrome patients (35). Six months of GHRT may improve sebum content which is reported to be decreased on the forehead (36). On the other hand, we also reported that GHRT in severely GH deficient patients, most of whom had Sheehan's syndrome, improves sympathetic tone which is decreased in severe GH deficiency, without an obvious arrhythmogenic effect (37).

Conclusion

We think that the prevalence of Sheehan's syndrome in the modern age, which is characterized by enormous development in health care and of course in obstetrical care, is underestimated. Two simple questions as to whether the patient failed to lactate and failed to resume menstruation after delivery are crucially important and these questions should be routinely asked when taking medical history. The most important thing is that doctors should be aware of Sheehan's syndrome. Thereby, most patients may be diagnosed promptly without delay. Otherwise, unrecognized and untreated patients may have increased morbidity and mortality due to chronic hypopituitarism.

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