Review Article

Sheehan's syndrome: Newer advances

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ABSTRACT

Sheehan's syndrome (SS) is postpartum hypopituitarism caused by necrosis of the pituitary gland. It is usually the result of severe hypotension or shock caused by massive hemorrhage during or after delivery. Patients with SS have varying degrees of anterior pituitary hormone deficiency. Its frequency is decreasing worldwide and it is a rare cause of hypopituitarism in developed countries owing to advances in obstetric care. However, it is still frequent in underdeveloped and developing countries. SS often evolves slowly and hence is diagnosed late. History of postpartum hemorrhage, failure to lactate and cessation of menses are important clues to the diagnosis. Early diagnosis and appropriate treatment are important to reduce morbidity and mortality of the patients.

Key words: Lactation failure, pituitary necrosis, postpartum hemorrhage, Sheehan

Introduction

Sheehan's syndrome (SS) occurs as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage [Figure 1]. Vasospasm, thrombosis and vascular compression of the hypophyseal arteries have also been described as possible causes of the syndrome. Enlargement of pituitary gland, small sellar size, disseminated intravascular coagulation and autoimmunity have been suggested to play a role in the pathogenesis of SS. SS is characterized by varying degrees of anterior pituitary dysfunction.[1] Some degree of hypopituitarism occurs in nearly one-third of patients with severe postpartum hemorrhage. Although symptomatic posterior pituitary function is uncommon, many patients have impaired neurohypophyseal function tests.[2] It is one of the most common causes of hypopituitarism in underdeveloped or developing countries. A recent epidemiological study from the Kashmir valley of the Indian subcontinent estimated the prevalence to be about 3% for women above 20 years of age, almost two-thirds of whom had delivered babies at home.[3] However, it is a rare cause of hypopituitarism in developed countries. In a study of 1034 hypopituitary adults, SS was the sixth most frequent cause of growth hormone deficiency GHD, being responsible for 3.1% of cases.[4] In a retrospective nationwide analysis in Iceland, the prevalence of SS in 2009 was estimated to be 5.1 per 100,000 women.[5] The aim of the present review is to discuss the recent advances in SS.

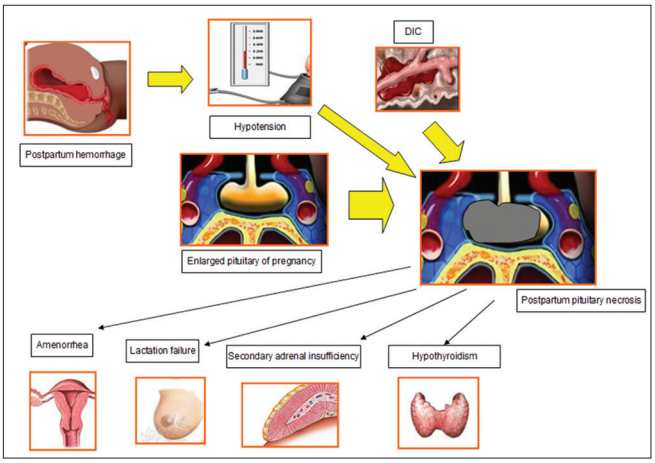

Figure 1: Pathophysiology of Sheehan's syndrome

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Presentation

SS can present in the postpartum period with lactation failure or after many months to years following the inciting

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delivery. In many affected women, anterior pituitary dysfunction is not diagnosed for many years. In a study of 60 patients, the average time between the previous obstetric event and diagnosis of SS was 13 years.[6] Characteristic manifestations include failure to lactate or to resume menses, genital and axillary hair loss, asthenia and weakness, fine wrinkles around the eyes and lips, signs of premature aging, dry skin, hypopigmentation and other evidence of hypopituitarism [Table 1]. The absence of amenorrhea or the presence of postpartum lactation, however, does not rule out the diagnosis. Uncommonly, it can present acutely with circulatory collapse, severe hyponatremia, diabetes insipidus, hypoglycemia, congestive cardiac failure or psychosis.[7-13]

The extent of anterior pituitary dysfunction varies in different series. The main involvement was the secretion of growth hormone (GH) and prolactin (90–100%), while deficiencies in cortisol secretion, gonadotropin and thyroid stimulating hormone (TSH) ranged from 50 to 100%.[6,14-19] At least 75% of pituitary must be destroyed before clinical manifestations become evident. GH deficiency is very common in SS because somatotrophs are located in the lower and lateral regions of the pituitary gland and are most likely to be damaged by ischemic necrosis of the pituitary.[20]

Anterior Pituitary Dysfunction

Lactation failure is a very common clinical feature and the lack of prolactin response to administration of thyrotropin releasing hormone (TRH) has been suggested as a sensitive procedure for screening of patients suspected to have SS.[21] Paradoxically, there are also reports of patients with hyperprolactinemia and galactorrhea.[22,23] Gonadotrophic function may be preserved in an occasional patient and there are several reports of patients with SS who maintained regular menstrual cycles and even became pregnant spontaneously.[24-26] Similarly, partial recovery of pituitary function has also been reported.[27]

Table 1: Clinical features of Sheehan's syndrome

History of postpartum hemorrhage
Lactation failure
Secondary amenorrhea, breast atrophy and decreased libido
Genital and axillary hair loss
Hypopigmentation
Signs of premature aging, fine wrinkles around the eyes and lips
Asthenia and weakness
Dry skin
Diabetes insipidus
Psychiatric disturbances, cognitive dysfunction
Changes in body composition
Anemia and pancytopenia
Hypotension and shock
Empty sella on MRI

Hyponatremia is the most common electrolyte disturbance occurring in 33–69% of all cases. Several mechanisms are responsible for hyponatremia. Hypothyroidism and glucocorticoid deficiency by decreasing free water clearance independent of vasopressin cause hyponatremia. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and volume depletion are the other factors leading to hyponatremia.[28-31]

Patients with SS and central hypothyroidism have low Free T3 (ft3) and Free T4 (ft4) with paradoxically normal or mildly elevated serum TSH. They, however, have severely blunted responses of TSH to acute TRH administration and no significant increase in serum TSH or ft4 levels after prolonged TRH infusion. This high level of TSH is due to increased sialylation (a form of glycosylation) which reduces its metabolic clearance leading to increased half-life. However, this glycosylated TSH has reduced biological activity as shown by TSH bioassay based on cAMP generation in a culture system of CHO cells transfected with recombinant human TSH receptor.[32] Abnormal circadian rhythm and increased total TSH secretion due to increased tonic non-pulsatile TSH secretion have also been described in these patients.[33,34]

Posterior Pituitary Functions

Clinical diabetes insipidus is apparently an uncommon complication of postpartum pituitary necrosis occurring in about 5% of all cases.[6,8,35-37] However, neurohypophyseal functions have been shown to be frequently impaired in SS even in patients without clinical diabetes insipidus. These include impaired osmoregulation of vasopressin secretion using hypertonic saline infusion test, higher serum osmolality during hypertonic saline infusion test and reduced maximum urine osmolality after water deprivation test. These changes are postulated to be due to the thirst center being affected by ischemic damage, leading to increase in the osmotic threshold for the onset of thirst.[2,38-41]

Hematological Abnormalities

Hematological abnormalities are common [Table 2] and

Table 2: Hematological abnormalities in Sheehan's syndrome

Anemia
Pancytopenia
Thrombocytopenia
Reduced PT and aPTT
Higher fibrinogen and d-dimer levels
?Acquired factor VIII and von Willebrand factor (aFVIII–VWF) deficiency
?Increased thrombophilic genetic mutations

include normocytic normochromic anemia, pancytopenia, and acquired factor VIII and von Willebrand factor (aFVIII–VWF) deficiency.[42] In a study of 40 patients with SS, anemia, thrombocytopenia and pancytopenia were described in 87%, 60% and 15%, respectively.[43] Anemia is believed to be due to deficient anterior pituitary hormones or absence of some other yet unidentified factors normally secreted from the pituitary. Pancytopenia is associated with hypocellular marrow and complete recovery has been shown to occur after achieving eucortisolemic and euthyroid state. Further, it has been shown that glucocorticoid replacement is more important than thyroxin replacement in reversing pancytopenia in these patients.[43-45] A shorter prothrombin time (PT) and activated partial thromboplastic time (aPTT), higher fibrinogen and d-dimer levels, and similar vWF activity were found in 32 patients with SS as compared with controls.[46] In another recent study, genetic mutations of FV-Leiden, FII G20210A, MTHFR C677T, MTHFR A1298C and PAI-1 4G/5G were found to be increased in 40 patients with SS compared to 45 controls. A significantly higher level of plasma total homocysteine (tHcy) than in the control group ($P < 0.001$) was also found in patients with SS.[47] This suggests that thrombhophilic mutations may predispose an individual to the development of SS.

Autoimmunity in Sheehan's Syndrome

The presence of anti-pituitary antibodies (APAs) has been demonstrated in some patients with SS, suggesting that an autoimmune pituitary process could be involved in this syndrome.[48,49] Hypothalamic cell anti-hypothalamus antibodies (AHAs), but not against arginine vasopressin AVP-secreting cells, have also been described. The significance of these antibodies is, however, unclear, but they may destroy the remaining pituitary cells with time. It is proposed that sequestered antigens due to tissue necrosis could trigger autoimmunity and may cause delayed hypopituitarism in these patients.[49] However, other studies did not detect APAs in this syndrome.[50]

Growth Hormone Therapy

Compared to patients with non-functional pituitary adenomas, those with SS are significantly younger at pituitary disorder onset, have significantly lower insulin-like growth factor I levels and more severe GH deficiency. GH replacement therapy (GHRT) in patients with SS has been shown to have beneficial effects on quality of life (QoL), body composition and lipid profile. However, no improvement in bone mineral density BMD was noted in a study of 14 severely GH-deficient patients with SS after 18 months of GHRT.[51-54] Golgeli *et al.* studied the impact of GHD and GH replacement therapy on cognitive function using P300 event related potential (ERP) latencies and found an impairment of cognitive abilities due to severe GHD in patients with SS and an improvement of cognitive function after 6 months of physiological GHRT.[55] In one study, GH-deficient females with SS had more non-rapid eye movement (NREM), particularly in stage 4 sleep, less rapid eye movement (REM) sleep and also less sleep efficiency when compared to healthy controls. After 6 months of GHRT, there was no significant difference in sleep parameters between them.[56] Increased cardiovascular mortality has been observed in patients with hypopituitarism including SS, and an adverse lipid profile, elevated body mass index (BMI), increased waist circumference, abnormal body composition, and a high risk of hypertension have been described.[4,57]

Radiology

The main radiological finding of SS is the image of an empty sella (around 70% of patients) or partially empty sella (30%). The time-dependent evolution of the findings on magnetic resonance (MR) imaging in SS has been described and begins acutely with nonhemorrhagic changes in signal intensity consistent with central infarction, along with peripheral and heterogeneous central enhancement in an enlarged pituitary gland. The findings are consistent with patchy central ischemic necrosis in an enlarged gland and are followed by pituitary gland atrophy and an empty sella. These findings on MR imaging characterize SS and provide early confirmation of the clinical diagnosis.[58]

Table 3 summarizes the clinical, laboratory, hormonal and radiological findings in five published case series of SS.

Treatment

The general principle of treatment of hypopituitarism holds good for the treatment of SS also. The goal of therapy is to replace deficient hormones. Treatment is important not only to correct endocrine abnormalities, but also to reduce mortality due to hypopituitarism.[1] In patients who have both secondary hypothyroidism and hypocortisolism, glucocorticoids should be replaced before the replacement of thyroid hormone. Gonadotropin deficiency and hypogonadism should be treated with a hormone replacement therapy.[1,21] Patients who wish to become pregnant may be directed to the service of fertility for ovulation induction followed by successful pregnancy. For patients with diabetes insipidus, treatment of choice is 1-desamino-8-D-arginine vasopressin or desmopressin (DDAVP).[21] Replacement of GH should be considered in patients with GH deficiency. Dosage of GH needs to be individualized. GH should be started on a low-dose regimen (0.1–0.3 mg/d) and titrated upward by 0.1 mg/d per month

Table 3: Clinical, laboratory, hormonal and radiological features in five published case series of Sheehan's syndrome

	Banzal *et al.*[19]	Sert *et al.*[15]	Dökmetaş *et al.*[17]	Ozkan *et al.*[18]	Gei-Guardia *et al.*[6]
No. of patients	30	28	20	20	60
Mean age at diagnosis (years)	38.5 ± 9.5	48.2 ± 10.5	60.15 ± 3.4	51.1 ± 9.4	45.8 ± 10.6
Time between inciting delivery and diagnosis (years)	<5: 33% 5–10: 40% >10: 27%	13.9 ± 6.1	26.8 ± 2.5	16.4 ± 4.7	13
History of PPH (%)	96.7	100	100	100	82
Failure to lactate (%)	100	93	70	100	67
Cessation of menses/amenorrhea (%)	100	86	100	100	73
Anemia (%)	NR	32	45	30	63.8
Hyponatremia	NR	32	35	NR	21
Hypopituitarism					
PRL deficiency (%)	93.3	95–100	100	65	69.2
Hypothyroidism (%)	96.7	100	90	75–100	80
GH deficiency (%)	NR	100	100	100	100
Secondary adrenal insufficiency (%)	90	100	55	100	96.6
Diabetes insipidus (%)	3	0	0	0	0
Empty sella on MRI/CT (%)	23.3	28	75%: complete 25%: partial	55%: complete 45%: partial	NR/incomplete data

PPH: Postpartum hemorrhage, GH: Growth hormone, PRL: Prolactin, NR: Not reported

with careful monitoring, so as to maintain insulin-like growth factor-1 levels within the age-appropriate range for the patient.[59] These patients may benefit from GH replacement, especially with regard to cardiovascular risk and body composition.

Conclusions

In conclusion, SS is a frequent cause of hypopituitarism in underdeveloped countries. The clinical features of hypopituitarism are often subtle and years may pass before the diagnosis is made following the inciting delivery. History of postpartum hemorrhage, failure to lactate and cessation of menses are important clues to the diagnosis. Early diagnosis and appropriate treatment are necessary to reduce the morbidity and mortality of patients.

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