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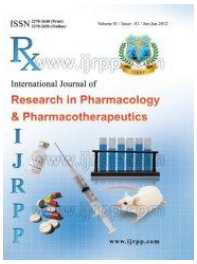

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Sheehan's syndrome- A review and update

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ABSTRACT

Sheehan's syndrome (SS) is postpartum hypopituitarism caused by necrosis of the pituitary gland. Sheehan's syndrome, though rare, is still one of the commonest causes of hypopituitarism in developing countries like ours. The clinical presentation is variable with abrupt or insidiously developing pituitary insufficiency after a heavy intra-partum or postpartum haemorrhage. It is usually the result of severe hypotension or shock caused by massive haemorrhage 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 haemorrhage, failure to lactate and cessation of menses are important clues to the diagnosis. Basal hormone levels may be enough in patients with typical histories, but most of the patients need more detailed investigation including dynamic pituitary function tests. 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. Pituitary MRI and CT may also be helpful for the investigation. Treatment of SS includes replacement of deficient hormone and the early diagnosis and appropriate treatment are important to reduce morbidity and mortality of the patients.

Keywords: Sheehan's syndrome, hypovolemia, sella, panhypopituitarism, adenohypophysis, Lactotrops hyperplasia, anti-pituitary antibodies (APAs), hormone replacement therapy

INTRODUCTION

Sheehan's syndrome, first described in 1937, is an adrenal pituitary insufficiency from hypovolemia secondary to excessive blood loss during or after delivery, it may present in post-partum period or several years after delivery[1].

PITUITARY GLAND

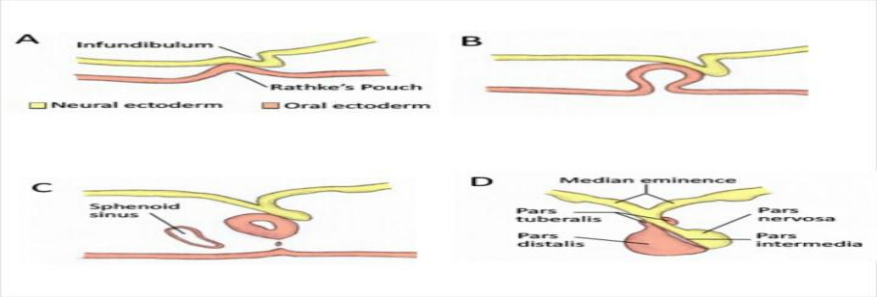
Pituitary is a gland about the size of small marble and is located behind the hypothalamus. It is also sometime called as the hypophysis. Pituitary gland consists of 2 functionally distinct structure that differ in embryonic development and anatomy; anterior pituitary (adenohypophysis) and posterior pituitary (neurohypophysis).

Anterior pituitary develops from rathke's pouch, which is an upward invagination of oral ectoderm from the roof of the stomodaeum, but the posterior pituitary develops from the infundibulum, which is a downward extension of neural ectoderm from the floor of the diencephalon.

Development of pituitary gland

A: Rathke's pouch and infundibulum develop from oral ectoderm and neural ectoderm, respectively. B: Rathke's pouch constricts at base. C: Rathke's pouch completely separates from oral epithelium. D: Adenohypophysis is formed by development of pars distalis, pars tuberalis, and pars intermedia; neurohypophysis is formed by development of pars nervosa, infundibular stem, and median eminence (figure 1)

Figure 1: Development of pituitary gland



The sellaturcica is the saddle like depression in the body of the sphenoid bone of human skull. It forms the bony seat for pituitary gland, Seat of the saddle is known as hypophyseal fossa, which holds the pituitary gland, (figure 2 and figure 3) [2].

Figure 2: Sellaturcica shown in green

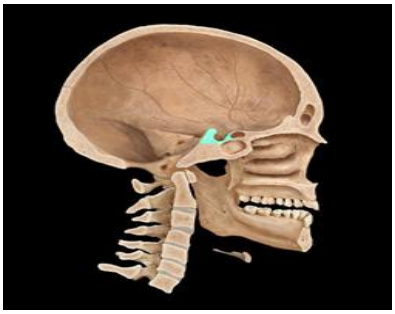
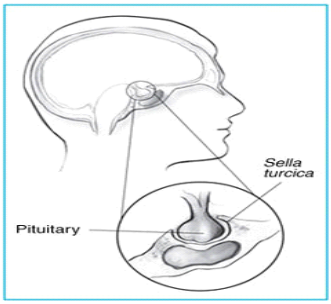


Figure 3: Pituitary gland in sellaturcica



HORMONES OF PITUITARY GLAND

Anterior pituitary gland produces several hormones which are important either to stimulate the target gland (such as adrenal, gonads, thyroid) to produce their corresponding hormones or directly affect the target organs. Adrenocorticotropic hormones (ACTH), gonadotropins, thyroid–stimulating hormones (TSH), growth hormone (GH) and prolactin are the major pituitary hormones. The gonadotropins comprise of luteinizing hormone (LH) and follicle-stimulating hormones. These 2 hormones regulate the production of female and male sex hormones as well as the germ cell i.e. egg cell and the sperm cell. The ACTH, gonadotropins and TSH act on other glands. Thus ACTH stimulates the adrenal cortex to produce corticosteroid hormones, mainly cortisol as well as male and female sex hormones in small amount. The growth hormone and prolactin directly affects their target organ.

GH is the most abundant among the pituitary hormones, it plays a major role in controlling the body`s growth and development. In addition it also affects carbohydrate and fat metabolism. Prolactin, together with other hormones plays a central role in initiation and maintenance of lactation. Release of prolactin from anterior pituitary is controlled by several factors, for e.g. prolactin is released in increasing amounts in response to the rise in oestrogen levels in the blood that occurs during pregnancy.

Posterior pituitary is not responsible for the production of its own hormones; instead it stores 2 hormone; vasopressin and oxytocin. They are produced by the neurons present in the hypothalamus and extend to the posterior pituitary[3]. Hormones secreted by anterior and posterior pituitary and their effect on target organs are given below in table 1 and 2.

Table 1: Hormones secreted by posterior pituitary

HORMONES	SECRETORY CELL TYPE	EFFECT
Oxytocin	Uterus and mammary glands	Uterine contraction and lactation
Vasopressin/Antidiuretic hormone(ADH)	Kidney and arteriols	Water retention and increased blood pressure

Table 2: Hormones secreted by anterior pituitary

HORMONES	SECRETORY CELL TYPE	TARGET	EFFECT
Growth hormone	Somatotrope	Liver and adipose tissue	Stimulation of growth and metabolism of carbohydrate and fat
Prolactin	Lactotrope	Mammary gland	Production of milk
Thyroid stimulating hormone	Thyrotrope	Thyroid gland	Secretion of thyroid hormones
Follicle stimulating hormone	Gonadotrope	Ovaries and testis	Regulates reproductive function
Luteinizing hormone	Gonadotrope	Ovaries and testis	Production of sex hormones
Adrenocorticotropic hormone	Corticotrope	Adrenal gland(cortex)	Secretion of glucocorticoid
Endorphin	Corticotrope	Opioid receptors	Inhibit pain perception

PITUITARY DISORDERS

Overproduction or under production of pituitary hormones will affect the respective end-organ. Acromegaly, Cushing`s disease, Sheehan's syndrome, Diabetes insipidus etc. are some of the disorder involving the pituitary gland.

During pregnancy pituitary gland is one of the most affected organs with altered anatomy and physiology. The pituitary gland is enlarged due to lactotroph hyperplasia and the demand of blood supply is increased. The interpretation of pituitary imaging and endocrinological tests are used for the evaluation of pituitary hormone deficiencies and hormone excess.

Acromegaly is a rare disease characterised by excess growth hormone secretion. In the reproductive age itself acromegalic women shows impaired fertilisation. Hyper prolactinemia is another disease of pituitary caused by a hormone secreting tumours. It causes galactorrhea, amenorrhea, and sterility in women. Diabetes insipidus is relatively a rare condition usually caused by hypo secretion of ADH. Pituitary insufficiency, Lymphocytic hypophysitis, Craniopharyngiomas, Cushing's disease, Sheehan`s syndrome etc. are some disease caused during pregnancy due to the altered anatomy and physiology of pituitary gland[4].

SHEEHAN'S SYNDROME

Sheehan's syndrome (SS) or post-partum pituitary necrosis is an adeno-pituitary insufficiency from hypovolemia secondary to excessive blood loss during or after the delivery. It was first described by Sheehan in the year 1937. Sheehan`s study was based on autopsy findings of the patient, who had died immediately after the delivery due to uterine bleeding[5].

The compression of blood supply due to an enlarged pituitary, severe hypotension, small sella size associated with postpartum haemorrhage makes the adenohypophysis more susceptible to ischemia in women[2]. Although the pathogenesis of Sheehan`s syndrome is not fully known, it is known that basic event is infarct in the anterior pituitary due to decreased blood volume, but it is not clear whether this infarct is due to vasospasm, thrombosis, or a vascular compression.

Sheehan's syndrome is a clinical state of panhypopituitarism resulting from severe post-partum hypotensive episode. SS may be acute or chronic, but its acute form is rarer. The diagnosis of

SS is usually made several years after the postpartum bleeding[6].

Infarcted areas may sometime are interspersed with perfused tissue, causing irregular pituitary enhancement, which is then leads to anterior pituitary atrophy[7].

Nearly one third of patient with severe postpartum haemorrhage shows some degree of hypopituitarism. Although symptomatic posterior pituitary function is uncommon, many patient show uncommon neurohypophyseal function tests.

The clinical manifestation of Sheehan`s syndrome varied from nonspecific symptoms like weakness, anaemia, dry skin, asthenia, fine wrinkles around the eyes and lips to severe pituitary dysfunction resulting in coma and death. Anaemia, pancytopenia, thrombocytopenia, increased thrombophilic genetic mutation, etc. are the common haematological abnormalities[8].

It is assumed that with better obstetric help the incidence and prevalence of SS has decreased especially in the developed countries. The current incidence and prevalence of SS is not fully known. SS is big health issue in underdeveloped countries where home delivery is practiced[9].

SS is believed to be one of the most frequent aetiology of GH deficiency. GH Deficiency is seen in almost all the patient, the level of other pituitary hormones like T3, T4, FSH, LH, etc. decreases in most cases.

Lactation failure is considered as the earliest manifestation and is seen in most of the patient. SS rarely accompanied with psychosis, acute renal failure, pancytopenia, diabetes insipidus and grave`s disease. Some studies also reveals that seizure, atherosclerosis, microprolactinoma are rare manifestation of Sheehan`s syndrome. Hypernatremia is an uncommon presentation of SS. The role of autoimmunity needs to be established in the pathogenesis of SS[10].

CT scans or MRI studies of pituitary gland have generally been done in the later course of Sheehan`s syndrome, and they have shown a non-haemorrhagic enlargement later the gland and empty sella may develops. Pituitary MRI is the most sensitive method of imaging, but CT scan may also be helpful[10, 11].

Treatment of SS includes replacement of deficient hormone, in severe pituitary insufficiency, glucocorticoid therapy may be helpful. L thyroxin is the drug choice for TSH deficiency[10].

DISCUSSION

EPIDEMIOLOGY

The current incidence and prevalence of SS is not well known in developed countries, SS is big health issue in underdeveloped countries. The prevalence of SS in India is estimated to be 2.5 to 4% among parous women older than 20 years. In the Kashmir valley of Indian subcontinent it is estimated to be 0.003% of total population has SS[12].

In an international database containing 1034 patient with GH deficiency, SS is the cause in 3.1% of the cases, SS is the culprit of GHD in 6-10% of the cases, in Spanish cross sectional studies[13].Retrospective study of the Iceland shows that prevalence of SS is 5.1 per 100000 women in Iceland[9].

MORTALITY AND MORBIDITY

The frequency of SS is decreasing world-wide; it is still frequent in underdeveloped and developing countries. Early diagnosis and appropriate treatment are important to reduce mortality and morbidity rate. In countries where surveys of maternal mortality have been conducted, it has been observed that deaths due to haemorrhage account for about 30% of all maternal deaths[14].Whatever be the cause mortality in the patient with hypopituitarism was significantly higher than in the general population[10].

ETIOLOGY

Sheehan's syndrome is one of the few hypopituitarism presentations, and necrosis of the pituitary gland is the rare complication of post-partum haemorrhage[15].

Pituitary gland is one of the highly vascularised tissues in the body; in pregnancy its volume increases 2 folds mostly due to massive hyperplasia of lactotrops as a result of elevated level of oestrogen secretion[16].

A Lactotrops hyperplasia start early in pregnancy and within several weeks to month after the end of pregnancy i.e., either delivery or abortion is then disappears. The height of the pituitary gland is about 0.08mm per week in the gestational period which seldom increases to more than 10mm during pregnancy[17].

The main causes of Sheehan's syndrome includes:

- Post-partum pituitary necrosis
- Compression of pituitary vessels due to relatively small sellaturcica volume associated with enlargement of pituitary during pregnancy

- Hypovolemic shock
- Placenta accreta, which is a reason for post-partum haemorrhage
- Arterial spasm due to severe hypotension that is due to massive uterine bleeding
- Disseminated intravascular coagulation (i.e. in amniotic fluid embolism and HEPP syndrome)[18]
- It has been identified as infarction and ischaemic necrosis that develops due to interruption of arterial blood flow in the anterior pituitary gland is the etio pathogenesis.

However the cause of interruption of blood flow is not clear. The autoantibodies detected against the pituitary gland have been suggested as a contributing factor in the development of Sheehan's syndrome in many cases. Pituitary autoimmune process could play a role in causing late complex pituitary dysfunction in female with SS[19].

PATHOPHYSIOLOGY

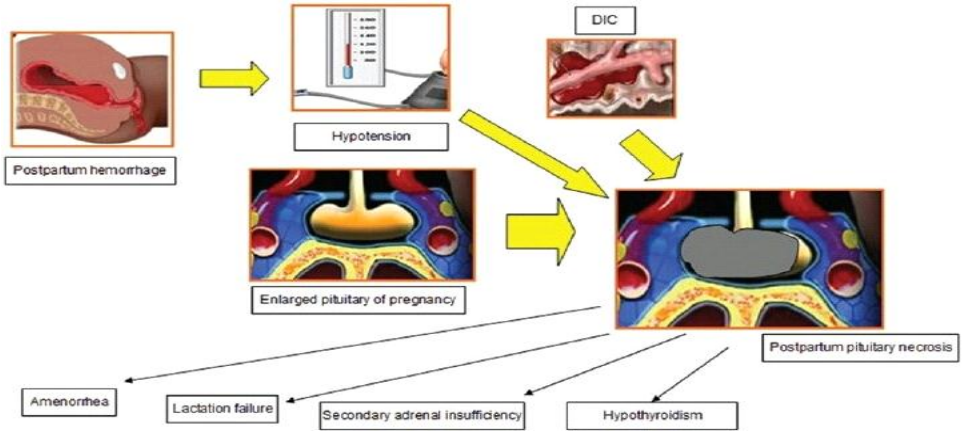
Hypertrophy and hyperplasia of lactotrops during pregnancy results in the enlargement of the anterior pituitary, and there is no increase in blood supply. Secondly, the anterior pituitary is supplied by a low pressure portal venous system.

These vulnerabilities, when affected by major haemorrhage or hypotension during the peri-partum period, can result in ischemia of the affected pituitary regions leading to necrosis. The posterior pituitary is usually not affected because of its direct arterial supply.

During pregnancy, there is an approximately 50% increase in the volume of the pituitary gland. Primarily this is due to hyperplasia of the lactotrops that secrete prolactin to prepare the breasts for lactation. Thus, whilst the volume of the pituitary increases, the fossa in which the pituitary gland rests does not increase to accommodate this growth. A sudden fall in blood pressure after an event like post-partum haemorrhage causes ischemia of the gland, cellular damage, and oedema. In turn, the oedema results in swelling of the pituitary gland (which is already enlarged by the lactotrops hyperplasia) further restricting the normal blood flow to the gland. The result is an infarct in the gland that causes loss of its secretions. This is initially manifest by failure of lactation and amenorrhea but may also variably demonstrate hypothyroidism (TSH) and hypoadrenalism (ACTH).

Three important clinical observations may be made. The first is that destructive lesions of the pituitary gland, they reduce secretions of anterior pituitary gland leading to hypopituitarism. The second is that the sequence of the loss of trophic hormones due to progressive lesions tends to be the same. Thus, somatotrophin-secreting cells are lost first, then gonadotrops, while the thyrotrophs seem to survive till last. The third is that such lesions rarely cause a deficiency of the posterior pituitary hormone secretions such as oxytocin and arginine vasopressin (AVP). Indeed, it is to be emphasized that the polyuria and intense thirst seen in some patients resulting from a deficiency of AVP (causing diabetes insipidus) was related to damage to the neural stalk or the hypothalamus and not to the pituitary gland (figure 4)[20,8].

Figure 4: Pathophysiology of SS



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. Hypothalamic cell anti-hypothalamus antibodies (AHAs) have

also been described, but not against arginine vasopressin AVP-secreting cells. The significance of these antibodies is, however, not clear, but they may destroy the remaining pituitary cells with time[19].

CLINICAL PRESENTATION OF SHEEHAN'S SYNDROME

Most common initial symptoms of Sheehan`s syndrome agalactorrhea and/or difficulty with lactation.

Clinical features of SS include

- Lactation failure
- Genital and axillary hair loss
- Secondary amenorrhea, breast atrophy and decreased libido
- hypopigmentation
- signs of premature aging; fine wrinkles around the eyes and lips, dry skin
- Asthenia, weakness, anaemia and pancytopenia
- Psychiatric disturbances, seizures
- Diabetes insipidus, hypotension and shock
- Empty sella on MRI

ANTERIOR PITUITARY DYSFUNCTION

Lactation failure is a very common clinical feature and the lack of prolactin response to administration of thyrotrophin releasing hormone (TRH) has been suggested as a sensitive procedure for screening of patients who have SS. There are also reports of patients with hyper prolactinemia and galactorrhea. Hyponatremia is the most common electrolyte disturbance occurring in most patients. Hypothyroidism and glucocorticoid deficiency resulted by decreasing free water clearance independent of vasopressin cause hyponatremia[8]. Hyponatrimea is not a disease; it is the only manifestation of hypopituitarism and hypothyroidism[21]. Post- partum hyperthyroidism is most common manifestation; aetiologies are thyroiditis (PPT) and GD[22].

Sudden drop of pituitary hormones due to postpartum haemorrhage may be responsible for some of the psychiatric symptoms. Levels of cortisol, oestrogen and thyroid hormones are decreased and these are implicated among main factors of psychiatric disorder. Anorexia nervosa, depression, and psychiatric disorders all are implicated among accompanying disease in hypopituitarism. There is no clear relation between psychiatric disorder and hypopituitarism yet. Some studies suggested that low levels of thyroid hormones and oestrogen as an aetiology of Sheehan`s syndrome[23].

A large proportion of patient with Sheehan's syndrome also have anaemia. Anaemia may develop due to cortisol insufficiency, hypogonadism and hypothyroidism[6].

POSTERIOR PITUITARY DYSFUNCTION

Clinical diabetes insipidus is apparently an uncommon complication of postpartum pituitary necrosis. 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, 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 centre being affected by ischemic damage, leading to increase in the osmotic threshold for the onset of thirst.

In recent studies growth hormone and prolactin deficiency is seen in 90 to 100% of cases. Cortisol, TSH, and gonadotropin were found to be decreased in 50 to 100% of cases. Acute cortisol deficiency can result in circulatory collapse and mortality if not detected. Loss of reproductive function, genital atrophy, loss of bone mineral density, weakness debility and premature aging may cause by deficiency of pituitary hormones[8].

Severe life threatening hypoglycaemia is a rare manifestation of SS. Hypoglycaemia with hyponatremia has been found more often in cases of acute SS. cortisol deficiency results in glycogen depletion leading to anorexia and weight loss. The glycogen depletion and low level of gluconeogenesis precursor (due to cortisol deficiency) results in impaired ability to tolerate fasting[24].

DIAGNOSIS

Diagnosis of SS can be difficult. Many of the symptoms overlap with those of other conditions. Diagnosis can be done by;

- Medical history
- Blood tests
- Pituitary hormone stimulation test
- Imaging tests[25]

The diagnosis of SS can be done by the physical examination and patient`s history and can be confirmed by laboratory tests (hormone level and hormone stimulation tests) which prove anterior pituitary failure.

Medical history include the information about child birth complication if any, patient may had, no matter how long ago the birth was given. It is based on clinical evidence of hypopituitarism in a woman with a history of a postpartum hemorrhage. Also diagnosed by evidence of whether there is lactation failure or failure of menstruation after delivery.

Deficiency of specific anterior pituitary hormones will show variety of symptoms. Corticotrophin deficiency can cause weakness, fatigue, dizziness, or hypoglycaemia. Gonadotropin deficiency often cause amenorrhea, oligomenorrheoa, hot flashes, or decreased libido[26].

Table 3: Hormone levels corresponding to the diseases

DISEASES	HORMONES							
	T3 (Normal-0.01-0.02 pmol/L)	Prolactin (Normal->20ng/ML)	T4 (Normal-29.6-54.0nmol/L)	Cortisol (Normal-4.3-22.4nmol/L)	FSH (Normal-4-9mIU/ml)	LH (Normal-4-9 mIU/ml)	GH (Normal <8.6ng/ml)	TSH (Normal-0.35 -5.5 µIU/mL)
Pancytopenia	0.011 mol/L	200.83pmol/L	<1.87nmol/L	<27.59nmol/L	9.9IU/L	5.3 IU/L7	-	2.03mIU/L
Hyperprolactenemia	0.5 ng/ml	50.52 µg/L	1.0µg/dl	1.96 µg/dl	14.83 iu/L	12.2IU/L	<0.25µg/L	11.24 µIU/ml
Diabetes insipidus	<0.3 µg/ml	10.47 µg/L	<1µg/dl	8.35µg/dl	6.53 IU/L	1.18 IU/L	0.25µg/L	3.31µIU/ml
Psychosis	49.3 µg/dl	-	2µ/dl	0.5 µ IU/ml	2.1 µIU/ ml	0.79 µ IU/ml	-	4.17 µIU/ ml
Hypelipoproteinemia	14 nmol/L	-	0.4nmol/L	-	-	-	-	3.5 mU /L
Congestive heart failure	-	12.1 ng/ml	O.4ng/dl	2.9 µg/dl	0.5 mIU/ml	0.9 m IU/ml	0.1 ng/ml	0.802 µIU/ml
Hypoglycaemia	0.011 pmol/L	200.83 pmol/L	<1.28nmol/L	2.26 pmol/L	9.9 IU/L	5.37 IU/L	-	2.03 mIU/L
Microprolactinemia	82.20 ng/dl	241 ng/ml	3.10ng/dl	-	7.51µIU/ml	4.30 µIU/ml	5.28 ng/ml	37.08µ IU/ml
Grave`s disease	13.06 pg/ml	-	2.14 ng/dl	12.99 mcg/dl	6.12 mIU/ml	5.66 mIU/ml	0.031 ng/ml	<0.0001m IU/ml
Seizures	-	-	0.77 ng/dl	2.69 µg/dl	2.38 U/L	2.08 U/ml	-	1.36µ IU/ml
Depressive disorder	-	0.86ng/ml	-	3.17µg/dl	3.0 mIU/L	0.42 mIU/ml	0.2ng/ ng/ml	3.12 mIU/L

Systemic pituitary evaluation can be performed by sequential pituitary stimulation test, consisting of insulin-induced hypo glycaemia followed by stimulation of gonadotropin, and thyroid-releasing hormone, metyrapone test, and adrenocorticotropic hormone stimulation test[27].

RADIOLOGICAL FINDINGS

The characteristic radiological finding of SS is the empty sella image (around 70% of patients) or partially empty (30%), as the presence of pituitary remaining is inversely related to the degree of hypopituitarism and the duration of the disease. Sellaturcica of small size has been reported as a common radiological finding in patients with SS, the small sella may be associated with the development of necrosis, because the pituitary increased compressed into a small space can undergo necrosis more easily during ischemia[8].

DIFFERENTIAL DIAGNOSIS

Other pituitary disorder associated with pregnancy can also result hypopituitarism. The differential diagnosis of Sheehan syndrome should be done with lymphocytic hypophysitis. Lymphocytic hypophysitis is a rare inflammatory disorder that results lymphocytic infiltration and destruction of normal pituitary tissue. The obstetric history is fundamental in SS, most of the time it will have a history of bleeding in the peri-partum period, which

does not occur in lymphocytic hypophysitis, while the presence of other autoimmune diseases suggests the diagnosis of hypophysitis which may be the presenting symptom[28].

Sheehan reported in his description of post-mortem examination of the pituitary glands that the lesion had the typical appearance of infarct and that are very thin layer of surface[11].

TREATMENT

Treatment for SS is lifelong hormone replacement therapy. The ideal treatment of Sheehan`s syndrome would be replacement of pituitary hormones by synthetic or natural product.

CORTICOSTEROIDS

drugs, such as hydrocortisone or prednisone, replace the adrenal hormones that aren't being produced because of an adrenocorticotropic hormone (ACTH) deficiency. During these times, body would ordinarily produce extra cortisol a stress hormone so dosage adjustment is necessary if the patient have flu, diarrhoea, or vomiting or have surgery or dental procedures. Adjustments in dosage may also be necessary during pregnancy or with marked weight gain or weight loss. Avoiding doses higher than need will eliminate the side effects associated with high doses of corticosteroids. Glucocorticoids stimulate the erythropoiesis[21].

E.g. Corticosteroid is added first-prednisone in the dose of 7.5 mg, 5 mg at morning and 2.5 mg in evening. This should be followed by addition of thyroxin, 0.075-0.15mg/day. Corticosteroid is replaced first because thyroxin therapy can exacerbate glucocorticoid deficiency and theoretically induce adrenal crisis.

LEVOTHYROXINE

This medication boosts deficient thyroid hormone levels caused by low or deficient thyroid-stimulating hormone (TSH) production.eg levoxyl, synthroid. Thyroid hormones stimulate erythropoietin production and proliferation of erythroid progenitor cells[25].

OESTROGEN AND PROGESTERONE

This may include oestrogen alone if the uterus is removed (hysterectomy) or a combination of oestrogen and progesterone if there is still uterus. To reverse genital atrophy, oestrogen and progesterone are given cyclically in case of microprolactinoma[16]. Oestrogen use has been linked to an increased risk of blood clots and stroke in women who still make their own oestrogen. The risk should be less in women who are replacing missing oestrogen. And while oestrogen replacement is available in either pills or patches, the patches seem to have a lower risk of side effects.

E.g. Conjugated oestrogen (0.65-1.25 mg/day) for 25 days and progesterone (5-10mg) on days 16 to 25 usually started on 7th day.

GROWTH HORMONE

Some studies have shown that replacing growth hormone in women with Sheehan's syndrome as well as in people with other forms of hypopituitarism can help normalize the body's muscle-to-fat ratio, lower cholesterol levels and improve overall quality of life. Side effects may include joint stiffness and fluid retention.

E.g. Somatotropin in the dose 0.1-0.125 mg /day

Similar improvement has been obtained by the administration of sodium chloride and gonadogen (pregnant mare`s serum), 20 units of gonadogen three times a week for two weeks, followed by an interval of two weeks and a repetition of the course[25].Use of thyroid extract is dangerous and may precipitate an adrenal crisis[29.]

Laboratory evidence of diabetes insipidus and clinical status of patient can be improved significantly with intranasal Desmopressin supplementation[30].

Table 4: Treatment for various manifestations of SS

DISEASE	DRUG
Depressive disorder	I.V. fluids (dextrose/normal saline) and hormone replacement therapy in the form of injection.
	Hydrocortisone (50 mg I.V. 6 hourly) and Thyroxin at a dose of 50 mcg/day[31].
Diabetes insipidus	1-desamino-8-d-arginine vasopressin or desmopressin (DDAVP)[32].
Hyperlipoprotenemia	Hydrocortisone (30mg/day)
	L-Thyroxin (150µg/day)[18]

Seizures	Cortisol and thyroxin replacement[33].
Hypoglycaemia	Saline infusion of 25% dextrose with hydrocortisone and levothyroxine[24].
Microprolactinoma	Dopamine agonist Bromocriptine and caberoline. Pituitary surgery to remove prolactinoma can successively cure hyper prolactinemia, but is expensive[34].
Psychosis	Combined dose of prednisolone and Levothyroxine[23]. The antipsychotics may be necessary as an adjunct in the initial stages if the patient show psychotic symptoms[35].
Grave`s disease	Antithyroid therapy in increased dose in addition, oestradiolvalerate and norgestral progestron therapy[36].

COMPLICATIONS

Adrenal crisis, a serious condition in which your adrenal glands produce too little of the hormone cortisol

- Unintended weight loss
- Menstrual irregularities
- Adrenal crisis: Life-threatening situation
- Low blood pressure.

The most serious complication is adrenal crisis, a sudden, life-threatening state that can lead to extremely low blood pressure, shock, coma and death. Adrenal crisis usually occurs when body is under marked stress such as during surgery or a serious illness and your adrenal glands produce too little cortisol, a powerful stress hormone. Because of the potentially serious consequences of adrenal insufficiency; it is recommended wearing a medical alert bracelet to indicate adrenal insufficiency[5, 25].

RISK FACTORS

Any condition that increases the chance of severe blood loss (haemorrhage) or low blood pressure during childbirth, such as having a problem with the placenta or being pregnant with multiples, may increase the risk of Sheehan's syndrome. Haemorrhage is a rare childbirth complication, however, and Sheehan's syndrome is even more uncommon. Both risks are greatly reduced with proper care and monitoring during labour and delivery[25]

MANAGEMENT OF POSTPARTUM HAEMORRHAGE

Uterine atony is responsible for most cases and can be managed with uterine massage in conjunction with oxytocin, prostaglandins, and ergot alkaloids. Retained placenta is a less common cause and requires examination of the placenta, exploration of the uterine cavity, and manual removal of retained tissue. Rarely, an invasive placenta causes postpartum haemorrhage and may require surgical management. Traumatic causes include lacerations, uterine rupture, and uterine inversion. Coagulopathies require clotting factor replacement for the identified deficiency. Early recognition, systematic evaluation and treatment, and prompt fluid resuscitation minimize the potentially serious outcomes associated with postpartum haemorrhage[37]

SUMMARY AND CONCLUSION

SS is one of the big health issues in underdeveloped countries. Even we are in a developing country SS was still reported and of Indian subcontinent it is estimated to be 0.003% of total population has SS. Sheehan`s syndrome is one of the few hypopituitarism presentations in which hyper prolactinemia is not a feature unless the infarction occurs within a prolactinoma. Although Sheehan`s syndrome is pregnancy related complication, notably it presents late as panhypopituitarism. Diagnosis is based on clinical evidence of hypopituitarism in a woman with history of post-partum haemorrhage. 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. CT and MRI play an important role in the diagnosis. Deficiency in anterior pituitary hormones causes variety of symptoms. The most important clue for diagnosis of SS is lactation failure and failure of menstruation resumption after delivery complicated with severe haemorrhage. Sheehan`s syndrome is associated with increased cause of mortality, weight loss, menstrual irregularities, low blood pressure, high serum cholesterol, acute adrenal crisis during stress and infection. Hormone replacement therapy is the only available treatment for SS. If there is lack of one or two hormones, the patient can survive with exogenous hormone administration. But if there is lack of several hormones, regular administration is not practical and still there is no treatment methodologies are implemented practically to overcome.

Typically in the replacement of damaged cells or tissues every month new applications are announced by using stem cells. The most recent application is the creation of pituitary gland tissue from the embryonic stem cells of mice. Self-formation of functional adeno hypophysis in three-dimensional culture have succeeded in not only creating pituitary gland tissue but also in transplanting the tissue successfully into mice with damaged pituitary glands and the results show that they mice recovered all or most of their pituitary output[38]. The above mentioned advancement may paw the way for the quality life of the patients with SS. After several trials, this may become successful in patients with SS.

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