

Sheehan's Syndrome: A Delayed Diagnosis

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Abstract: Sheehan's syndrome is a condition characterized by hypopituitarism secondary to ischaemic necrosis of pituitary gland. In Sheehan's syndrome necrosis occurs due to hypotension and shock resulting from massive postpartum haemorrhage. This disease is becoming rare now due to better postpartum care but is still prevalent in developing countries especially in rural areas and if occurs, it often develops slowly which can be missed and a delayed diagnosis increases mortality and morbidity in affected individuals. Here we present a case of a 37 year old female who presented at our institute with complaints of fever and generalised weakness. She had not attained menses for last 15 years. Patient gives history of post-partum haemorrhage and scanty lactation in her last pregnancy which was 15 years back. Patient was evaluated and a diagnosis of Sheehan's syndrome was made. In this case patient was diagnosed after 15 years of disease onset this calls for a better understanding of the disease and prompt identification of clues like failure to lactate or absent menstruation following postpartum haemorrhage.

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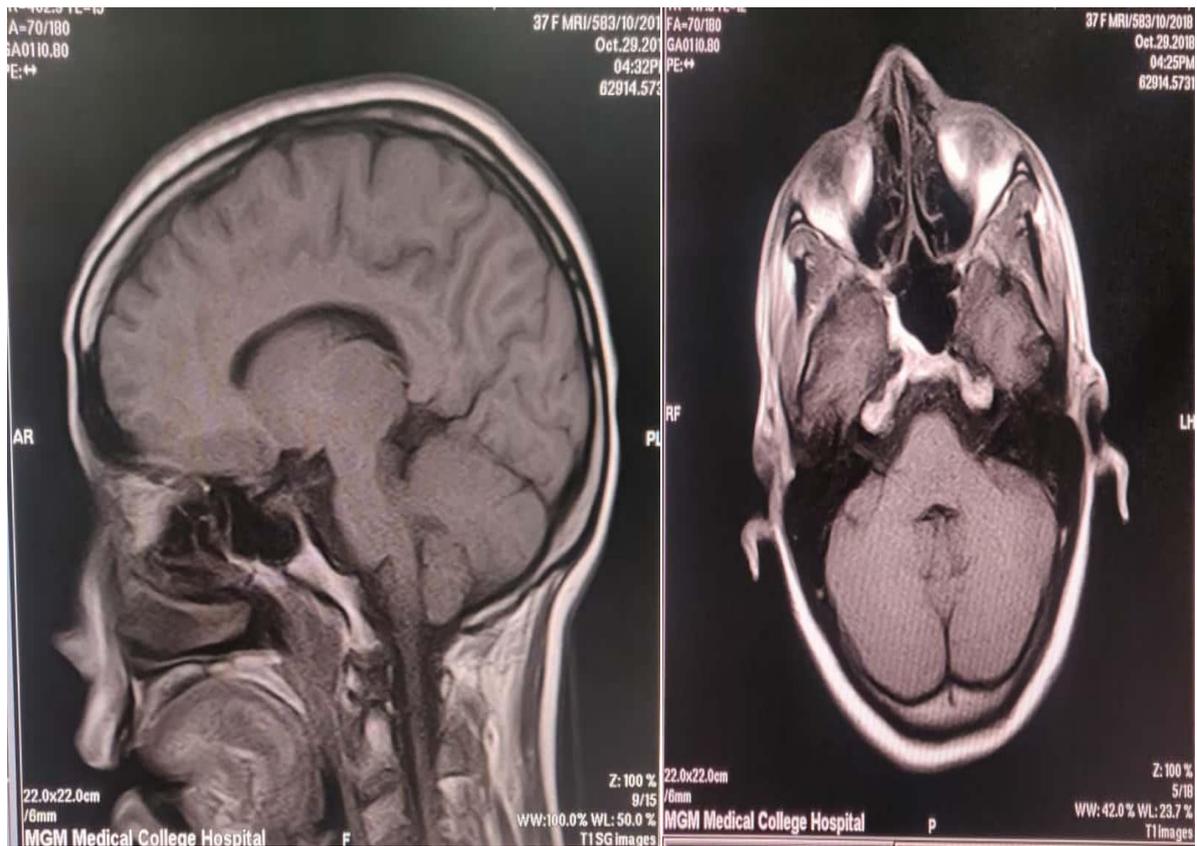
I. Introduction

60% cases of hypopituitarism are due to Pituitary tumours and their treatments while 30% of hypopituitarism cases have a non-tumour origin. Sheehan syndrome explains 6% of all causes of hypopituitarism. This syndrome was first described by Sheehan in 1937 as Deficiency of anterior pituitary hormones resulting from infarction and necrosis of the physiologically enlarged pituitary gland of pregnancy, usually preceded by postpartum haemorrhage which leads to arterial spasm in smaller vessels, apoplexy and subsequent pituitary necrosis.

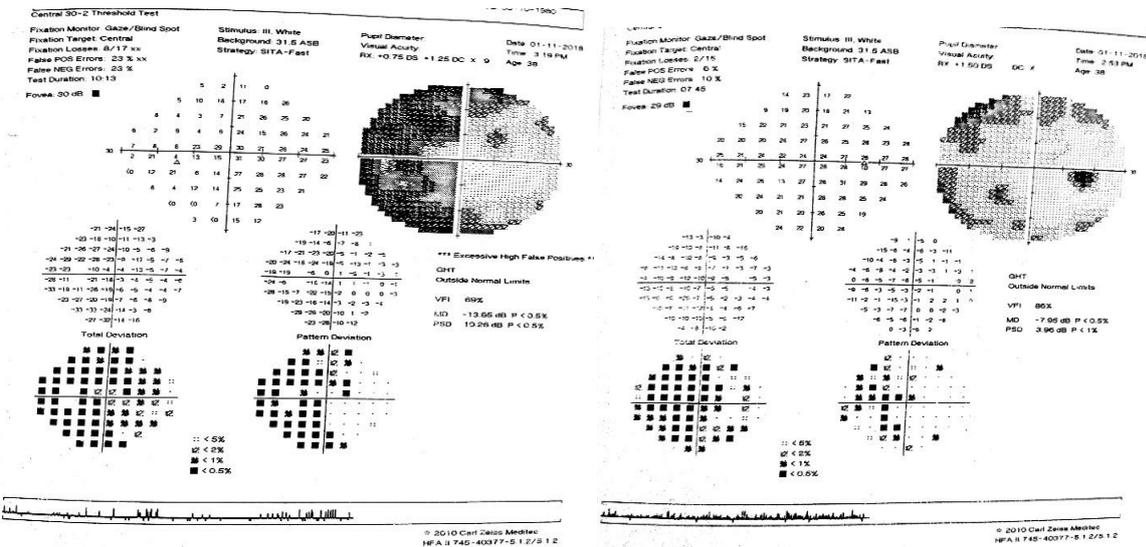
II. Case Report

A 37 year old female presented in our institute with history of low grade fever, generalized weakness and lethargy. On taking detailed history the patient revealed that her last menstrual period patient says that she has not attained menses from last 15 years since her delivery. Her first delivery was a male child full term normal delivery at home without any complications in post-partum period however in her second delivery patient says she had massive bleeding due to retained placenta which was removed after around 12 hours. Patient was taken to a primary care hospital where she was treated with IV fluids and blood transfusion. Patient also had scanty lactation in that pregnancy for first month after which she failed to lactate. On examination patient was vitally stable, had mild pallor and had no axillary hair with scanty pubic hair, Breast Tanner was stage 2. The patient was suspected to be a case of Sheehan's syndrome and was worked up for the same.

MRI BRAIN was suggestive of cerebro spinal fluid collection in pituitary fossa with non-visualization of pituitary gland suggestive of empty sella



VEP studies done s/o bilateral hemianopia which can be due to ischemic injury to optic chiasma



LAB INVESTIGATIONS

- HB 9.6 g/dl (reduced)
- TLC 4000 per micro liter (normal)
- Platelet 3.31 lakhs per micro liter (normal)
- Normocytic normochromic type of anemia on peripheral smear
- LFT normal in range
- RFT normal in range

Lipid Profile normal in Range
Sodium 132 (reduced)
Potassium 3.3 (reduced)
TSH 0.23 million international units per liter (low)
T4 3.2 micro liter per deciliter (low)
FSH 1.08 mIU/L (low)
LH 1.09 mIU/L (low)
PROLACTIN 46.44 mIU/L (low)
ACTH (8 AM) 8 pg/ml (low)
Cortisol (8 AM) 7micro gram/ml (low)

III. Discussion

First described by Sheehan in 1937 as Deficiency of anterior pituitary hormone resulting from infarction and necrosis of the physiologically enlarged pituitary gland of pregnancy, usually preceded by postpartum haemorrhage which leads to arterial spasm in smaller vessels, apoplexy and subsequent pituitary necrosis

In pregnancy there is a increased hormonal demand leading to enlargement of pituitary, there is 45% enlargement in the first trimester and pituitary becomes 120–136% of its original size near term and has its highest volume during the first few weeks of the postpartum period and regain its normal size, shape and volume within 6 months following delivery. Due to this Increased demand and compression of the vasculature of the gland there is increased vulnerability of gland to Ischemia, due to PPH.

The clear pathogenesis of Sheehan syndrome remains uncertain. Not every patient has a history of massive PPH nor does every massive PPH lead to Sheehan syndrome. Confounding factors that affect the initiation and progression of the disease, are severity and spread of necrosis, age of the patient, history of previous births associated with PPH, number of births, Autoimmune component and genetic predisposition. Although restricted pituitary blood supply following untreated severe hypotension associated with pph is the most common cause for the development of Sheehan's syndrome. Predisposing factors for restricted pituitary blood supply are Pituitary gland enlargement, Small size sellaturcica, and arteriolar vasospasm due to hypotension, Thrombosis and coagulation abnormalities. Frequency of genetic mutations of coagulation factor V, II methylenetetrahydrofolate reductase and plasminogen activator inhibitor type 1, is increased in patients with Sheehan syndrome compared with the general population. Disease initiate as necrosis of the anterior lobe due to infarction/arrest of blood flow/vasospasm/ thrombosis/arterial compression. Depending on the size and site of necrosis; pituitary hypo function results in deficiency of hormones. If >50% of pituitary gland remains intact; functions remain intact and if >70% is affected it leads to partial or pan hypopituitarism. This disease is characterized by slow progression of pituitary dysfunction, even several years after the initial insult this may be because of Sequestered antigens due to tissue necrosis could trigger autoimmunity and may cause delayed hypopituitarism also percentage of cells that express both CD3 and DR1 are increased in individuals and is suggestive of an ongoing inflammation accompanying the slow progression of pituitary dysfunction. Characteristic of necrosis is that Adenohypophysis cells are replaced by necrotic debris, coagulated blood, inflammatory cells and ghost cells which leads to scarring and ultimately atrophy (empty sella). Patients can present with symptoms ranging from isolated hypopituitarism to pan hypopituitarism. GH and Prolactin are the most commonly affected hormones causing fine wrinkling around mouth and lactation cessation. FSH and LH deficiency leads to amenorrhoea/oligomenorrhoea/loss of libido. TSH loss can cause weight gain, constipation, cold intolerance etc. ACTH loss can cause weakness, fatigue, weight loss, hypotension and hypoglycaemia. Posterior lobe can also be affected rarely, leading to diabetes insipidus. Sheehan syndrome can also result in severe clinical outcomes such as adrenal crisis, circulatory collapse, myxoedema coma and hyponatraemia and can lead to death if not properly treated. In haematological manifestation occurs Anaemia which is generally normochromic normocytic, can be hypochromic microcytic or rarely macrocytic. This is due to Cortisol and thyroid hormone deficiency leading to decrease in the synthesis of erythropoietin or by decreasing the biological effects of endogenous erythropoietin. Bone marrow hypoplasia and pancytopenia can occur; both are reversed after the replacement of deficient hormones. Coagulation disorders can be diagnosed by measuring adaptive factor VIII and von Willebrand factor deficiencies, decreased Prothrombin time and activated Prothrombin time, and an increase in the levels of fibrinogen and d-dimer.

PREVENTION

WHO has guidelines for the prevention of PPH, which include a combination of interventions, such as cord clamping and cutting (within 1–3 minutes), controlled cord traction and use of an uterotonic agent such as oxytocin, misoprostol. Anaemia during pregnancy should also be corrected and emphasis on minimum interventions during delivery should be made.

MANAGEMENT

In Acute adrenal insufficiency glucocorticoid treatment should be started immediately after taking a serum sample for the measurement of cortisol and ACTH levels. Dose should be titrated as per clinical findings instead of laboratory results. To approximate the circadian rhythm of endogenous cortisol production dual-release hydrocortisone tabs given once daily. Lifelong therapy is required in these patients. Patients should be informed about increasing their daily dose in some situations such as infection, surgery and trauma.

Levothyroxine should be given (75-150 mcg). Titration of dose depends on fT4 and fT3 levels rather than on TSH levels. When hypothyroidism and hypoadrenalism occur together, thyroid hormone therapy should follow glucocorticoid replacement to avoid adrenal crisis as GH therapy increases conversion T4 to T3, thus increasing LT4 dose requirement.

Use of oestrogen and progesterone is Controversial. Replacement therapy is usually recommended in premenopausal women with Sheehan syndrome, unless there is a contraindication such as DVT, PE, severe cirrhosis, active viral hepatitis and uncontrolled severe hypertension. Oral oestrogen should be avoided in patient on GH therapy.

Opinions about efficacy and the routine use of GH treatment are divided because of the risk– benefit ratio and cost-effectiveness. Different trials show benefits of using GH such as improved body composition and the lipid profile, improved cognitive function, improves sympathetic tone without an obvious arrhythmogenic effect.

Ovulation induction can be used in women who want to become pregnant, although some patients can have spontaneous pregnancies. When pregnant, regular follow-up to adjust glucocorticoid doses is needed. Levothyroxine doses also need adjustment whereas GH therapy should be stopped.

There are no data about the replacement of Prolactin during gestation and the postpartum period for lactation in Prolactin deficient patients

IV. Conclusion

Most patients with Sheehan syndrome have nonspecific symptoms, such as weakness, cold intolerance, anaemia and feeling unwell, which affect Quality of life especially because of long diagnostic delay. These patients thus remain undiagnosed or misdiagnosed for a long time and receive inappropriate treatments. Increased awareness of this condition will result in earlier diagnosis and hence better Quality of life, and lower morbidity and mortality.

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