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Research Article

Abnormal Liver Functions in Sheehan Syndrome, a Needle to Non-Alcoholic Steatohepatitis: An Observational Study

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Abstract

Background: Sheehan Syndrome (SS) refers to the occurrence of hypopituitarism after parturition classically due to pituitary necrosis. Some degree of hypopituitarism has been reported in 32% of women with severe postpartum hemorrhage. The extent of pituitary damage determines the rapidity of onset as well as magnitude of pituitary dysfunction. Liver involvement in hypopituitarism arise owing to Growth Hormone (GH) deficiency. The metabolic conditions and liver function have improved by the administration of GH.

Materials and Methods: Thirty patients with Sheehan's Syndrome (SS) and thirty age and Body Mass Index (BMI) matched controls were part in this study. All patients were stable on conventional replacement therapy for at least 6 months before the study. The subjects underwent detail clinical, biochemical, and hormone analysis. Patients with SS with deranged liver function were referred to me for treatment if required and for observation.

Results: Patients with Sheehan's syndrome, on conventional replacement therapy, referred to me showed significantly higher alanine transferase levels (p = 0.009) and alkaline phosphatase levels (p = < 0.001) of significance compared with controls.

Conclusion: This observational study showed abnormal liver functions in Sheehan's syndrome patients compared to age and BMI matched controls. It can an early pointer of steatosis in these patient and may warrant follow up for excluding SS as an endocrine cause of steatohepatitis.

Keywords: Sheehan syndrome; Liver functions; Non- alcoholic steatohepatitis

INTRODUCTION

Sheehan's Syndrome (SS) is defined as pituitary hormone deficiency due to ischemic infarction of the pituitary gland as a result of massive postpartum uterine hemorrhage [1]. The physiological enlargement of the pituitary gland during pregnancy plays a significant role in onset of SS, because severe bleeding does not lead to pituitary deficiency in women unless they are pregnant. Even though the pathogenesis of SS has not yet been fully clarified, the basis of its pathology has been identified as infarction and ischemic necrosis that develops due to the interruption of arterial blood flow in the anterior pituitary gland [2]. It is one of the most common causes of hypopituitarism in underdeveloped or developing countries. Studies have shown that in females Sheehan's is still most common cause of hypopituitarism as was seen in Turkish population [3]. 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 [4]. The metabolic changes that accompany hypopituitarism are central obesity, hyperlipidemia, and insulin resistance. These metabolic changes are principally thought to be due to GH deficiency, although altered insulin-like growth factor-1, cortisol, and gonadotropin metabolism have also been implicated [5-7]. Various changes have been seen to occur during pregnancy. Alteration in liver functions are known to occur in cases involving vasoconstriction of hepatic vascular bed [8]. Adult patients with anterior pituitary deficiency and associated GH deficiency have fatty infiltration of the liver more frequently than patients with anterior pituitary hormone deficiency without GH deficiency [9]. It has been reported that in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and lifestyle-related diseases based on Growth Hormone (GH) deficiency associated with hypopituitarism, these metabolic conditions and liver function were improved by the administration of GH [10]. In addition, thyroid dysfunction is observed in approximately 25% of patients with NAFLD [11]. These findings suggested that endocrine hormonal abnormalities are closely related to the development of NAFLD. All patients were on corticosteroid replacement, which is a known cause of liver steatosis. However, it is rare for corticosteroid-induced steatosis to progress to steatohepatitis. Furthermore, the dosing of corticosteroid used in our patients was physiologic, replacing absent endogenous corticoids. Thus it is unlikely this physiologic dosage of corticosteroids had a significant role in the development of steatohepatitis. More over liver dysfunction (rise in the level of ALT and AST) has been in patients with hypopituitarism [12,13], though data on liver function abnormality in SS is meagre.

MATERIALS AND METHODS

Thirty Sheehan syndrome patients and thirty age and Body Mass Index (BMI) matched controls took part in study. Patients were recruited from Endocrine clinic of internal medicine at Government medical college, Srinagar. Around thirty voluntary age and BMI matched healthy controls were included in our study and were recruited from hospital staff and friends. A written well-informed consent was obtained from all patients and controls and the study was performed according to the Declaration of Helsinki, 1975. These patients were on follow-up and were on treatment for more than 6 month. The diagnosis of SS was based on history of postpartum hemorrhage and/or failure of lactation and/or amenorrhea following last child birth, more than one anterior pituitary hormone deficiency and empty sella on MR imaging. Fasting early morning (08:30 am) blood samples were collected for glucose, Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), cortisol, Thyroid Stimulating Hormone (TSH), total T4, Prolactin (PRL), and GH and measured by Immune Radiometric Assay (IRMA). In addition, anthropometric measurements were taken and venous blood samples were also collected in separate containers for routine hematological, kidney and liver function tests and were analysed using techicon DAX-72 autoanalyser in the central biochemistry laboratory, Government medical college Srinagar. The study was conducted over a period of 2 years.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± SD, median, and interquartile range categorical variables were summarized as percentages. Chi-square test or Fisher's exact test, whichever appropriate, was used for comparison of categorical variables. Graphically the data were presented by bar and pie diagrams. *P* value of less than 0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

Out of the 30 studied patients, 15 belonged to the age group of 40-49 years (50%), whereas only 5(16.7%) and 8 (26.7%) patients

belonged to age groups 30-39 years and 50-59 years respectively. Only 1 patient was aged above 60 years. These cases were matched with healthy controls with mean age of patients and controls was 47.7 ± 4.47 years and 47.3 ± 4.34 years, respectively. The interval between the beginning of disease and definitive diagnosis varied between 1 and 20 years with a mean of 11.35 ± 4.47 years. The detail of the clinical profile is given in table 1. Of the 30 Studied cases, 16 (53.33%) had a BMI in the normal range, that is, (18.5–22.9), 10 patients (33.33%) were overweight (BMI 23–24.9), and only 4 (13.3%) were obese (BMI of >25). The cases were matched with healthy controls with a mean BMI of 22.76 ± 1.98 in cases and mean BMI of 22.14 ± 1.64 in controls (Table 2). Hormone levels were below normal for FSH in 40% of patients, LH in 60%, TSH in 52%, GH in 89.9%, PRL in 72%, Cortisol in 84% and FT4 in 49.8% of patients. Out of 30 patients, 26.7% patients had ALT values within normal range <40 IU/l while as 73.3% had values > 40 IU/l compared to control group with 60% had values <40 IU/l and 40% had >40 IU/l (p = 0.009). Similarly, 76.7% of patients had an ALP value >150 IU/l whereas 23.3% had normal values (<150 IU/l). In comparison, only 26.7% of patients had above normal ALP values and 73.3% had normal values. A statistically significant difference was seen between two groups (p = < 0.001). However bilirubin, AST and Albumin showed no significant statistical difference between two groups is shown in table 3.

DISCUSSION

Sheehan's syndrome which was first described by HL Sheehan classically refers to postpartum hypopituitarism due to pituitary necrosis occurring during severe hypotension or shock secondary to massive bleeding at or just after the delivery [1]. Patients with hypopituitarism have the feature of metabolic syndrome, including central obesity, insulin resistance, and dyslipidemia. Because metabolic syndrome, including insulin resistance, is the main pathogenesis of the development of Nonalcoholic Fatty Liver Disease (NAFLD) [14]. The pathophysiologic mechanism of insulin resistance in patients with hypopituitarism is not known with certainty, but available evidence suggests that interaction between growth hormone and leptin may play a role. Growth hormone is regulated by nutrients and metabolites, such as Free Fatty Acids (FFA), triglycerides, glucose, and amino acids [15]. Although the etiology of leptin resistance in pituitary disease remains unclear, it is probable that low levels of growth hormone and insulin-like growth factor-1, which occur in most patients with hypopituitarism (75% in this study), result in loss of feedback within the hypothalamo-pituitary-adipose axis, thus creating a hyperleptinemic state. Growth hormone causes lipolysis, resulting in increased FFA and possibly leptin levels [16]. Hyperleptinemia, which occurs in hypopituitarism may contribute to NAFLD by enhancing adipocyte production of proinflammatory cytokines, such as tumor necrosis factor-, that may be hepatotoxic, [17] and by inducing insulin resistance in hepatocytes through dephosphorylation of insulin-receptor substrate 1 [18]. In cases of GH deficiency associated with hypopituitarism, the prevalence of liver fat deposition in the abdominal echo is generally approximately 60%; the frequency of fatty liver is high compared to that in general populations [19]. Growth hormone was administered to the patients with lifestyle-related disease, and it enhanced their metabolism and energy consumption. The improvement of liver function after GH administration is considered to be due to improvements in the patient's metabolic and energy consumption state [20]. Growth hormone is also expected to be useful as a treatment strategy aimed at the metabolic and energy improvement of general NAFLD patients in the future.

In our study, we observed that the ages of the patients ranged between 35 and 62 years with mean age of patients and controls was 47.7 ± 4.47 years and 47.3 ± 4.34 years, respectively. The interval between the beginning of disease and definitive diagnosis varied between 1 and 20 years with a mean of 11.35 ± 4.47 years. All patients were on stable replacement therapy of thyroxine and steroids for mean duration of 1.5 years±6months (range: 6 months to 8 years). None of patients had received growth hormone replacement. Similar observation were made by Yusuf Ozkan, et al. [21] who found that mean age of patients was between 40 to 65 years with a mean age of 51.12 +/- 9.44 years (mean +/- SD). Time to make a definitive diagnosis of the disease ranged between 5 and 25 years with a mean of 16.35 +/- 4.74 years. We also studied liver function tests in the two groups and found that results were comparable in the two groups studied (except for the liver enzymes aspartate transaminases) with 26.7% patients had Alanine Transaminase (ALT) values within normal range <40 IU/l while as 73.3% had values > 40 IU/l compared to control group with 60% had values <40 IU/l and 40% had >40 IU/l (p = 0.009). Similarly, 76.7% of patients had an Alkaline Phosphatase (ALP) value >150 IU/l whereas 23.3% had normal values (<150 IU/l). Similar observation have been made by Ebenezer AN, et al. [22] who found that Hypopituitary patients had higher elevations in serum aminotransferase levels and hyperbilirubinemia-24% versus 11% (p < 0.01), as well as higher International Normalized Ratio (INR) and hypoalbuminemia 40% *versus* 23% (p < 0.01). There is an increased prevalence of metabolic syndrome and liver dysfunction consistent with NAFLD in hypopituitarism. Hong JW, et al. [23] studied

Table 1: Clinical profile of patients.

Parameters	Number of cases	Percentage
History of post partum hemmorrhage	27	90%
Failure of lactation	25	83.33%
Secondary ammenorrhea	30	100%
H/O blood transfusions	12	40%
Empty sella on MRI	11	36.67%
Duration of treatment	1.5 ± 6 Months	

Table 2: Distribution of BMI among cases and controls.

BMI (Kg/M²)	Cases		Controls		p- value
	No.	% age	No.	% age	
<18.5	0	0	0	0	0.192
18.5-22.9	16	53.33	17	56.67	
23-24.9	10	30.3	10	30.3	
> = 25	4	13.3	3	10	
Mean ±	22.76 ± 1.98		22.14 ± 1.64		

Table 3: Prevalence of abnormal LFT in Sheehan's syndrome patients.

LFT	Cases (% age)	Controls (% age)	p- value
Bilirubin (mg/dl)	13.3	23.3	0.504
AST (IU/l)	36.7	13.3	0.074
ALT (IU/l)	73.3	40	0.009*
ALP (IU/l)	76.7	26.7	<0.001*
Albumin (mg/dl)	20	16.7	0.889

*Statistically significant difference (p < 0.05)

the metabolic parameters and nonalcoholic fatty liver disease in hypopituitary men. And found that the NAFLD is more common in hypopituitary patients than control subject. Also severe growth hormone deficiency in hypopituitarism was associated with the severe degree of hepatic steatosis in NAFLD.

CONSENT

Informed consent was obtained from patients for study.

AUTHOR STATEMENT

This study was approved by the ethics committee of GMC Srinagar 190010, J&K India.

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