Lurking in the Shadows

Hypopituitarism is a common diagnosis in endocrine clinics throughout the world. The causes of hypopituitarism can be varied, but in developing countries, Sheehan syndrome (SS) is an important aetiology. SS refers to postpartum hypopituitarism due to necrosis of the pituitary gland. Most cases of SS are a result of severe hypotension after postpartum haemorrhage.[1] Other factors such as small sellar size, pituitary antibodies, and coagulation abnormalities may also contribute to the ischaemic insult.[2] The advances in obstetric care have reduced the incidence of postpartum haemorrhage dramatically in developed countries.[3] As a consequence, SS is now considered to be a rare cause of hypopituitarism in developed countries. Back in 2009, only 5 in 1,00,000 women in Iceland were affected by SS; this number might have dropped further by now.[4] On the contrary, data from Kashmir, India, suggest that at least 3–4% of parous women in the reproductive age group may be suffering from SS.[5] However, even in India, the prevalence seems to vary. In urban India, SS may have become less common; a study in a tertiary care hospital in Delhi reported that SS contributed to 5% of the hypopituitarism cases.[6] On the contrary, a study from Himachal Pradesh reported that SS contributed to nearly 60% of hypopituitarism cases.[7] The diagnosis of SS can be delayed up to 13 years postpartum, indicating that a significant proportion of SS patients remain undiagnosed.[8] The diagnosis is often made when the patients present with acute complications related to hypopituitarism.[9,10] Patients with SS can present with variable hormonal deficits. Although panhypopituitarism is usual, preservation of gonadotrophs and corticotrophs is possible.[11] Although the typical patients with SS present with anterior pituitary hormone deficits and preservation of posterior pituitary function, the literature indicates that involvement of posterior pituitary can also occur. There are at least eight case reports of SS presenting with frank central diabetes insipidus.[12-15] In a study, the water deprivation test was able to identify partial diabetes insipidus in nearly 30% of patients with SS, while the osmotic threshold for onset of thirst was found to be increased.[16] Similar abnormalities have been reported earlier as well.[17] Hence, the evaluation of posterior pituitary function in SS is justified. However, the water deprivation test is cumbersome and uncomfortable to the patients, many of whom may be asymptomatic with respect to posterior pituitary defects. In this issue, Laway *et al*.,[18] have attempted to address this aspect by using basal and hypoglycaemia-stimulated copeptin levels to diagnose posterior pituitary dysfunction. They were able to identify diabetes insipidus in 9% of the SS cases, with half of them having partial DI. Furthermore, studies in this area will help in defining simpler protocols to screen for posterior pituitary function in SS patients.

While the acute hazards of undiagnosed hypopituitarism are obvious implications of undiagnosed SS, research on SS has brought to light several additional aspects that contribute to long-term morbidity and mortality in SS. The bone health of patients with SS is also adversely affected, presumably as a consequence of untreated hypogonadism.[19] Osteopenia and osteoporosis in SS have been reported in as high as 41% and 35% of the cases, respectively.[20] The bone texture imaging parameters in patients with SS are altered, indicating that the bone trabecular pattern is affected and the overall bone mineral density (BMD) may be low.[21] However, a recent study, using high-resolution peripheral quantitative computed tomography, has reported that despite reductions in BMD, the bone microarchitecture is preserved in patients with SS.[22] The low BMD in SS patients can improve significantly after oestrogen replacement and correction of calcium and vitamin D deficiencies.[23] Patients with SS have been reported to develop pleural and pericardial effusions and sometimes even cardiac tamponade.[24] In untreated patients with SS, nearly half of the patients have pericardial effusion, mitral regurgitation, and reduced left ventricular mass. However, upon achieving euthyroid and eucortisol states, these cardiac abnormalities appear to resolve.[25] The quality of life in SS patients may be worse as compared to controls. In a small study from India, the patients with SS performed worse in physical and psychological health domains of quality of life scores, although the overall scores were comparable to controls.[26] Both metabolic syndrome and impaired glucose tolerance occur more frequently in patients with SS as compared to controls.[27] Nonalcoholic fatty liver disease is quite common in SS with a large percentage of cases having severe hepatic steatosis.[28] The effects of SS on the vascular system are also interesting. Untreated SS patients have narrower arterial diameters and reduced flow-mediated dilatation and nitric oxide (NO) increment as compared to controls; these abnormalities appear to improve after treatment. However, baseline and stimulated NO levels remain higher in SS patients compared to controls, irrespective of treatment.[29]

Although extensive data on SS are lacking, patients with hypopituitarism are likely to die earlier as compared to healthy populations and cardiovascular diseases are the most common cause of death.[30] Available literature suggests that patients with SS are predisposed to coronary artery disease. Markers of coronary artery disease such as high-sensitive C-reactive protein (hsCRP), apolipoprotein B (ApoB), and lipoprotein A [Lp(a)] are significantly higher in patients with SS as compared to controls. More than 50% of SS patients have coronary artery calcification as compared to just 7% of controls, while around 5% of SS patients are at

high risk for coronary events (versus none in the control).[31] In another study, an Agatston score of greater than 10 was present in 75% of SS cases as compared to none in the controls.[32] While inflammatory markers such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are elevated in patients with SS, the elevation has been reported to be higher in those affected by psychological disorders.[33] Leptin levels may be elevated in SS patients compared to controls.[34] An abnormal lipid profile has been reported in SS as compared to age and weight-matched controls. The lipid profile in SS was characterised by elevated total cholesterol, triglycerides, and low-density cholesterol along with lower high-density cholesterol. These lipid abnormalities are at least partly attributable to growth hormone deficiency (GHD). GHD causes upregulation of the 11beta HSD-1 enzyme, leading to the conversion of cortisone to cortisol. GH replacement causes significant improvement in lipid abnormalities in SS.[35] GH therapy can also improve visceral adiposity and the carotid intimal medial thickness. The contribution of prolactin to the CV risk in SS has not been quantified till now. In the general population, it appears that abnormalities in prolactin levels are associated with hypertension, obesity, dyslipidaemia, insulin resistance, and atherosclerosis.[36,37] Low prolactin levels correlate with higher levels of inflammatory cytokines.[38] Furthermore, prolactin receptors are present on atherosclerotic plaques, and both locally and systemically secreted prolactin may affect plaque stability and plaque progression.[39] However, data on cardiovascular mortality and prolactin have been inconsistent. Recently, a study found that in patients with diabetes, higher prolactin levels were associated with mortality.[40]

In this issue, Agrawal *et al*.[41] studied in detail the entire spectrum of cardiovascular risk factors in 45 patients with SS. Interestingly, they found that among lipid parameters, only triglycerides were elevated in the SS patients when compared to controls. Even the prevalence of metabolic syndrome and dysglycaemia in SS was not higher than in controls. These findings point towards the high prevalence of diabetes and metabolic syndrome in the country. Despite this, the SS patients had a higher waist circumference (at comparable BMI), elevated inflammatory markers, and CIMT, indicating the additional risk imposed by SS on a population that is predisposed to metabolic diseases and already suffering from the onslaught of modern unhealthy lifestyles. Since GHD contributes to a large chunk of this additional risk, the cost factor and parenteral route of administration ensure that a vast majority of SS patients will not receive GH replacement. Indian SS patients may probably have cardiovascular morbidity and mortality far exceeding that seen in developed countries. Considering the still high prevalence of SS in the country and the associated high CV risk, aggressive management of SS with a focus on the treatment of the cardiovascular risk factors and efforts to provide GH replacement to SS patients is the need of the hour.

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Website: https://journals.lww.com/indjem/

DOI: 10.4103/IJEM.IJEM_239_24

How to cite this article: Raizada N, Madhu SV. Lurking in the shadows. Indian J Endocr Metab 2024;28:229-31.