CASE REPORT

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Rare Case of Acquired Factor IX Deficiency in a patient of Sheehan Syndrome

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Summary

Sheehan syndrome due to ischaemic infarction of the pituitary gland as a result of massive post-partum haemorrhage is characterised by varying degrees of anterior pituitary dysfunction. Its incidence has declined in the developed countries in parallel with improved obstetrical care. But its prevalence is still high in developing countries. Vasospasm, thrombosis and vascular compression of the hypophyseal arteries, enlargement of pituitary gland, small sellar size, DIC and autoimmunity are suggested as pathogenetic factors of this syndrome. We report here a case of a 45-year-old lady who had prolonged bleeding after dental extraction requiring referral and treatment at a tertiary care centre (BHU), 3 months prior to being diagnosed as a case of Sheehan syndrome with acquired factor IX deficiency, at our centre. Pure tone audiometry documented bilateral moderate-to-severe mixed hearing loss which significantly improved after correction of her hypothyroidism. She had suffered severe post-partum haemorrhage during her last delivery 15 years back which was followed by failure of lactation, non resumption of menstruation and generalised weakness, lethargy, malaise and progressive hearing impairment over this period. Her factor IX deficiency, hyponatraemia, and hyperkalaemia got corrected along with improvement in lipid profile and transaminitis after normalisation of thyroid and adrenal dysfunction with thyroxine and prednisolone. She resumed her normal household activities with treatment. Only two other cases of Acquired factor IX deficiency, including one associated with pancytopenia have been reported in literature. The purpose of reporting this case is to increase awareness about this very rare, easily treatable but difficult to diagnose clinical condition which is still prevalent in many developing countries.

Key words: Sheehan syndrome, factor IX, empty sella, hypopituitarism, post-partum haemorrhage.

Introduction

Sheehan syndrome (SS) is defined as pituitary hormone deficiency due to ischaemic infarction of the pituitary gland as a result of massive post-partum uterine haemorrhage[1]. It is a rare clinical condition, with much higher prevalence in developing countries with poor obstetrical services as compared to developed nations. Estimated prevalence of SS is 3.1% among women in the Kashmir valley vs 5.1 per 1,00,000 women in Iceland[2,3]. SS presents clinically with subtle and partial pituitary hormone deficiency symptoms with resultant delay of many years in their diagnosis and treatment[4]. The average time between the previous obstetric event and diagnosis of SS was 13 years in a study of 60[5]. Some very rare manifestations, like acquired Factor IX (FIX) deficiency or pancytopenia have been reported in SS[6,7]. Unawareness about their association with SS may be the reason for paucity of literature about these manifestation. For this very reason we report here a case of 45-year-old lady who was diagnosed as a case of SS. She had a bout of severe dental bleeding after tooth extraction due to acquired FIX deficiency. She was diagnosed as a case of Sheehan syndrome after retrograde review of her medical history and after perusing clues from clinical examination and laboratory investigations on her presentation to our Medical OPD with unrelated clinical features of acute respiratory infection with spasmodic bronchitis.

Case report

A 45-year-old lady presented to the Out Patient Department of our tertiary care hospital with history of moderate grade fever with chills lasting for 3 - 4 days about 2 weeks back. It was associated with generalised body aches, throat irritation, dry cough and anorexia. It subsided with use of antipyretics prescribed by her family doctor. Currently she was afebrile. There was no history of haemoptysis, wheezing, shortness of breath, diarrhoea, rash, arthralgias, dysuria, hematuria, oliguria. On examination, patient was noticed to be conscious, co-operative, oriented, but dull looking middle-aged lady, who was poorly communicative on account of progressive hearing impairment over last few years. Her blood pressure was 128/79 mmHg, pulse was 64/min, regular, respiratory rate of 16/min and spo2 of 99% on ambient air, her BMI (weight in kilograms divided square of height in meters) was 25 kg/M^2. Face was pale, mildly puffy with paucity of facial expressions. Sclerae were anicteric, mucous membranes were moist, with no thyromegaly/thyroid tenderness, neck vein engorgement

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or lymphadenopathy. Mild non pitting oedema was noticed on the feet and shins bilaterally. Skin was dry and rough in texture. There were few scattered ronchi bilaterally in the chest. Other systemic examination was essentially normal without any focal neurological deficit or musculo-skeletal abnormalities.

Patient was prescribed tablet montelukast, levocetrizine and terbutaline plus ambroxil syrup for her current symptoms. She was advised complete haemogram, kindney, liver and thyroid function tests along with lipid profile and urine routine examination and a follow-up visit was scheduled after 1 week. Results of these investigations are given in Table I. Significant findings were very low FT4 with normal TSH levels, severe hyponatraemia with mild hyperkalaemia, significant dyslipidaemia and mild transaminitis with normal glycaemic profile, CBC and body iron stores. Because of very low T4 levels with inappropriately normal TSH, secondary hypothyroidism due to pituitary dysfunction was suspected and patient was advised serum cortisol, ACTH, prolactin, LH, FSH and IGF-1 levels. Results of these investigations are given in Table II. Her 8AM serum cortisol was low with inappropriately normal ACTH, along with low serum IGF-1 and prolactin levels. Her gondotrophin levels were also inappropriately low for a patient of menopausal age with long standing amenorrhoea. MRI of the brain revealed Empty Sella with loss of anterior pituitary but preserved posterior pituitary signal on T1 weighted imaging. On reviewing her medical history in detail she gave history of prolonged bleeding lasting for 2 - 3 days after dental extraction 3 months back for which she had to be hospitalised into a tertiary care hospital. Her hearing loss had worsened further after this episode of dental bleeding. There was no history of ear discharge, vertigo, tinnitus or pain in the ear currently or in the past. Patient was not taking any anti platelet or oral anticoagulants. There was no past history of easy bruising, gum bleeds, epistaxis, haematemesis, malena or haemoarthrosis or any bleeding disorder in her maternal family or her progeny. On further questioning patient gave history of severe post-partum haemorrhage with loss of consciousness following her last childbirth 15 years back, which required multiple blood transfusions. In the puerperium she had lactation failure and never had normal menstrual periods following that. She has continued to be have progressive vague asthenia and general ill health and loss of libido since then along with gradually progressive hearing loss which turned out to be bilateral moderate-to-severe mixed hearing loss on Pure Tone Audiometry. Patient's aPTTK was 46.4 seconds (control 28 seconds) with normal platelet count, PT INR, FDP and factor VIII levels (FVIII). FIX levels however were 30 % of normal (70 - 120%). Based on clinical history, physical examination findings and laboratory investigations suggestive of hypopituitarism and empty sella on MRI brain, diagnosis of Sheehan syndrome with Factor IX deficiency was made. She was prescribed thyroxine 50 mcg/day to be gradually increased to 100 mcg over next 4 weeks. This was preceded by prednisolone 20 mg/day for 1 week followed by gradual tapering down by 2.5 mg/week to 7.5 mg of prednisolone once daily. Patient came for follow-up after 2 months. Her physical condition had improved dramatically. She was now very physically active, looking after all house-hold work efficiently. Her hearing had also improved significantly. Her thyroid functions and serum electrolytes became normal. Dyslipidaemia and transamintis had also improved. Factor IX levels, PT INR, aPTTK also normalised (Table II). Gonadotropin levels were unchanged as no treatment was prescribed for that, as patient did not desire so.

Table I: Routine laboratory parameters at presentation and 2 months after treatment.

Investigation		Before treatment	After treatment	Ref range
CBC	Hb	11.9	12.7	12 - 15 gm/dl
	RBC	3.89	4.07	3.8 - 4.8 10^{12}/l
	MCV	89.2	94.1	83 - 101 fl
	TLC	6.9	8.3	4 - 10 10^{9}/l
	Platlets	185	183	150 - 410 10^{9}/l
Iron profile	Iron	111		28 - 170 µg/dl
	TIBC	338		261 - 478 µg/dl
	TS	32.84%		17 - 37%
	Ferritin	302		11 - 306 ng/ml
	Transferrin	255		200 - 360 mg/dl
KFT	Na	117	136	136 - 144 meq/L
	K	5.4	4.9	3.6 - 5.1 meq/L
	Urea	12	13.8	15 - 38 mg/dl
	Creatinine	0.63	0.50	2.6 - 6.0 mg/dl
	Uric acid	1.8	3.4	2.6 - 6.0 mg/dl
LFT	SGOT (AST)	114	48.5	15 - 41 IU/L
	SGPT (ALT)	43	112.9	14 - 54 IU/L
	ALP	233	95.2	32 - 91 IU/L
	GGTP	59	119.3	7 - 50 IU/L
	Total protein	7.7	6.5	6.5 - 8.1 g/dl
	Albumin	4.49	3.7	3.5 - 5.0 g/dl
	Bilirubin	1.2 mg/dl	0.68	0.8 - 1.2 mg/dl
Lipids	Total cholesterol	333	267	< 200 mg/dl
	Triglycerides	196	103.4	150 mg/dl
	LDL	244	182.8	130 mg/dl
	HDL	29	73.3	50 mg/dl

Table II: Hormones and coagulation factors at presentation and after 2 months of treatment.

Investigation		Before treatment	After treatment	Ref range
Thyroid	TSH	2.66	1.37	0.34 - 5.6 µIU/ml
	T3	2.1	3.46	2.6 - 4.2 pg/ml
	T4	0.14	0.94	0.58 - 1.64 ng/ml
Hormones	Cortisol 8 am	3.99		6.7 - 22.6 µg/dl
	Cortisol 4 pm	3.7		2 - 15 µg/dl
	ACTH	25.9	16.8	0 - 46 pg/ml
	Prolactin	3.13	8.59	3.34 - 26.74 ng/ml
	IGF1	25.9		53 - 331 ng/ml
	FSH	6.98	3.2	3.85 - 8.78 mIU/ml
	LH	1.93	3.59	2.12 - 10.89 mIU/ml
Coagulation	Factor IX	30	96.3	70 - 120%
profile	Factor VIII	106	175	50 - 150%
	FDP	< 5		< 10 µg/ml
	aPTTK	46.4	29.9	(Control 28 sec)
	PT	13.2		12.1 - 15.1 sec
	INR	1.16	0.96	

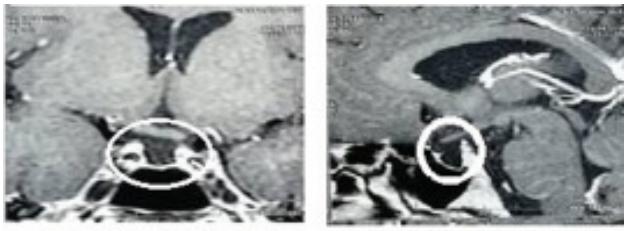

Fig. 1: *Showing empty Sella turcica in coronal (thin circle) and Sagittal (thick circle) views on T-1 weighted MR imaging.*

Discussion

Sheehan syndrome is defined as pituitary hormone deficiency due to ischaemic infarction of the pituitary gland as a result of massive post-partum haemorrhage and is characterised by varying degrees of anterior pituitary dysfunction. Vasospasm, thrombosis and vascular compression of the hypophyseal arteries, enlargement of pituitary gland, small sellar size, DIC and autoimmunity have been suggested as pathogenetic factors of SS[1]. Its incidence has declined in the developed countries in parallel with improved obstetrical care. But its prevalence is still high in developing countries. Zargar *et al* estimated the prevalence of SS to be 3.1% among women in the Kashmir valley India[2]. In Iceland, the prevalence of SS in 2009 was estimated to be 5.1 per 1,00,000 women[3]. Majority of SS patients are diagnosed with a clinically subtle partial pituitary deficiency symtoms and signs and therefore their diagnoses and treatments are delayed for many years[4]. Average time between the previous obstetric event and diagnosis of SS was 13 years in one study of 60 patients[5]. Commonest clinical presentation is lactation failure in the immediate post-partum period followed by non resumption of menstruation, loss of libido, breast atrophy, decrease in axillary and pubic hair, lassitude and lack of energy gradually over the years. Fine wrinkles around the eyes and lips, signs of premature aging due to growth hormone deficiency, dry and rough skin due to hypothyroidism and hypopigmentation due to ACTH and MSH deficiency are other manifestations, which appear in a more subtle way over the ensuing years. Some rare manifestations, like Factory IX deficiency (FIX) or pancytopenia have been reported in SS[6,7]. Rarely acute catastrophic presentation with circulatory collapse, severe hyponatraemia, diabetes insipidus, hypoglycaemia, or psychosis may occur[8-11]. At least 75% of pituitary must be destroyed before clinical manifestations become evident. GH deficiency is very common in SS and hyponatraemia is the most common electrolyte disturbance occurring in 33 - 69% of all cases[12]. Clinical diabetes insipidus is an uncommon complication of post-partum pituitary necrosis occurring in about 5% of all cases[6,8]. Several mechanisms are responsible for hyponatraemia, including hypothyroidism and glucocorticoid deficiency which act by decreasing free water clearance, independent of vasopressin[13,14].

While this patient's recent bleeding episode after dental extraction could have been due to low FIX levels, her post partum haemorrhage leading to SS possibly arose out of obstetrical causes because there was no family history of any bleeding disorders including haemophilia. Haemophilia carriers (females) generally have adequate levels (> 60%) of clotting F VIII or F IX which are sufficient to control bleeding after trauma. However, clotting factor levels can vary from one carrier to another due to lyonisation[15]. Bleeding symptoms in carriers correlate very closely with the carrier's plasma concentrations of FVIII or FIX. Women with a clotting factor level of 40% or below are three times more likely to report prolonged bleeding after surgical operations as compared to those with clotting factor levels of above 40%[16,17]. Our patient was not a carrier of haemophilia as the male child born out of her last delivery did not manifest any bleeding tendencies suggestive of haemophilia. In spite of that she had FIX levels of 30% at presentation which got corrected to 96% along with normalisation of hyponatraemia and hyperkalaemia with treatment of her thyroid and adrenal deficiency with steroids and thyroxine over the next two months suggesting

SS as possible cause of FIX deficiency and the resulting bleeding after dental extraction.

Endocrine coagulopathy is a well reported entity. There is growing evidence of several abnormalities of the coagulation and fibrinolytic systems in patients affected by thyroid, pituitary, parathyroid, PCOS, and metabolic syndrome. Clinically overt hypothyroidism appears to be associated with a bleeding tendency due to aVWD type 1, whereas all other endocrine and metabolic disorders appear to be associated with a thrombotic tendency. Bleeding tendency in such patients is rapidly reversible after pharmacologic treatment of the hormonal dysfunction especially hypothyroidism and adrenal deficiency[18]. First case of bleeding with factor IX deficiency in SS was reported in 1972 by Clarence H. Brown *et al*, in a patient whose clinical presentation was similar to our patient[6]. After thorough investigations and trials of various combinations of FFP as well as use of thyroxine and cortisol in isolation, in sequence or in combination, these investigators concluded that hypothyroidism and hypoadrenalism in patients of SS can result in FIX deficiency with bleeding tendency after surgical interventions. Our patient also had evidence of secondary hypothyroidism and hypoadrenalism and FIX deficiency , the latter being the possible reason for her bleeding after dental extraction. Only two other cases of factor IX deficiency in SS patients including the one with associated pancytopenia have been reported in literature[6,19]. All these cases including our case had complete correction of FIX deficiency after treatment with thyroxine and prednisolone. Diana Lang *et al*[19] who reviewed the published literature on association of pancytopenia with SS came across a total of only 21 published cases majority of which (15 out of 21), were reports of Sheehan's syndrome. Our patient, in addition had significant improvement of hearing acuity after replacement therapy with prednisolone and thyroxine. Her Pure Tone Audiometry (PTA), which had shown bilateral moderate-to-severe mixed hearing loss at presentation, showed only mild conductive loss on repeat testing after 2 months of treatment. Hearing insufficiency, due to dysfunction at multiple levels such as endocochlear, retrocochlear or central hearing pathways, has been reported in 36 out of 69 hypothyroid patients in two studies[20,21]. Like our patient, L-thyroxine therapy resulted in variable improvement of hearing in 48% of ears, with complete restoration of hearing in 15% of them as reported by Mohammed *et al*[22].

Conclusion

Acquired FIX deficiency is a rare manifestation of SS which can present unsuspectingly as severe bleeding after surgical interventions in patients with FIX levels of < 40% of normal. This along with pancytopenia, another rare manifestation of SS are easily reversible with replacement of deficient anterior pituitary hormones, especially with thyroxine and corticosteroids. Hearing dysfunction also improves with correction of hypothyroidism. These observations have been scantily reported in literature because SS itself is a rare and difficult to diagnose condition with very subtle and partial anterior pituitary dysfunction which manifests years after the post-partum haemorrhage. Increased awareness of this easily correctable coagulopathy, may be helpful in preventing catastrophic bleeding after surgical interventions. It may also lead to preventive screening of SS patients for factor IX deficiency and more frequent reporting of such cases, resulting in increasing awareness about this entity.

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