Teaching Round

Fatiguability, Asthenia and Body Swelling in a Young Female

Arunkumar R Pande, Amit Kumar

Abstract

A 32 year female presented with easy fatiguability, asthenia and generalised swelling of 8 years duration. Past history revealed a home delivery 8 years back complicated with post partum haemorrhage. Lactation failure and secondary amenorrhoea followed this delivery. Examination revealed a delayed ankle reflex. Hormonal profile suggested panhypopituitarism. A diagnosis of Sheehan's syndrome was made. Sheehan's syndrome, a rare complication of post-partum haemorrhage, is often missed and mean duration between start of disease and diagnosis usually is 5-8 years. Hence, a high index of suspicion and awareness of this entity is important.

Key words: Sheehan syndrome; edema; hypopituitarism

A 32 year old housewife, P1L1A0 presented to Medicine emergency department with chief complaints of insidious onset and progressive easy fatiguability, asthenia and swelling of body since 8 years. Despite several visits to the Medicine outpatient department she did not have alleviation of symptoms. Examination revealed a pale-looking patient with generalised oedema, vitals were stable and systemic examination was unremarkable except for a delayed ankle reflex.

What differential diagnosis will you consider in a patient who presents with insidious onset and progressive complaints of easy fatiguability, asthenia and swelling of body?

Chronic complaints of easy fatiguability, asthenia and generalised swelling can be witnessed as a presenting feature of any systemic disorder. In a young female in our Indian scenario, it is important to consider anaemia, connective tissue disorders like systemic lupus erythematosus (SLE), rheumatoid arthritis, viral infections, tuberculosis, HIV infection, various malignancies, drug side effects, psychiatric disorders, and endocrinological diseases like hypothyroidism (myxoedema), hypopituitarism and Addison's disease.

Anemia is one of the commonest differentials which may alone or associated with some other disorder present with this symptom complex. Polymyalgia rheumatica, fibromyalgia and chronic fatigue syndrome are also possible differentials. Hypothyroidism can present as easy fatiguability but features of menstrural abnormalities in the form of oligomenorrhoea or menorrhagia and alteration in bowel habits in the form of constipation are common accompaniments. Examination in a patient with hypothyroidism usually shows bradycardia, diastolic hypertension, croaky voice, dry and coarse skin. Delayed ankle reflex can be present. Hypothyroidism can be present as a part of other polyglandular syndromes. Polymyalgia rheumatica is closely associated with giant cell arteritis and presents as easy fatiguability. Isolated polymyalgia rheumatica is a clinical diagnosis made by the presence of typical symptoms of stiffness, aching and pain in the muscles of hip and shoulder girdle, easy fatiguability, an elevated ESR, absence of clinical features of giant cell arteritis, and a prompt therapeutic response to low dose prednisolone. Fibromyalgia is characterised by chronic widespread musculoskeletal pain, stiffness, parasthesiae, disturbed sleep and easy fatiguability along with multiple painful tender points, which are widely and symmetrically distributed. Chronic fatigue syndrome is characterised by debilitating fatigue and several associated physical, constitutional and neurophysiological complaints.

Department of Medicine, Lady Hardinge Medical College & SSK Hospital, New Delhi, India.

Corresponding Author: Arunkumar R Pande, Department of Medicine, Lady Hardinge Medical College & SSK Hospital, New Delhi-110001.

Received : 03-05-2010 | Accepted : 08-07-2010 | Published Online : 15-07-2010

What history is important in this case?

In a young female presenting with constitutional symptoms, following history specifically needs to be paid attention to-

1. nutritional history to ascertain iron and calcium/vitamin D deficiency
2. worm infestations (iron deficiency anemia and malnutrition)
3. menstrual history (important for hypothyroidism, infections and rheumatologic disorders)
4. skin rash, photosensitivity, oral ulcers, arthralgias, joint swellings (rheumatologic disorders)
5. history of abortions, still-births/foetal wastage (collagen vascular diseases and infections)
6. fever (non-specific complaint)
7. change in skin or oral pigmentation (anemia and Addison's disease)
8. history of promiscuity (HIV, sexually transmitted infections and depression)
9. Symptoms for Tuberculosis and HIV and associated infections can be varied and atypical at times.
10. Mental and psychiatric assessment.

Interestingly detailed history revealed that patient had amenorrhoea since first conception. Obstetric history was pertinent in this case. her full term delivery, conducted at home by an untrained dai, was complicated by post partum haemorrhage. The patient had developed severe paleness and had to be transfused blood, although no documented haemoglobin report was available. History of failed lactation was also present. How is this piece of information relevant in this case?

It is very important to realise that pregnancy conducted by an untrained dai and complicated by post-partum haemorrhage requiring blood transfusion is a not-so-infrequent occurrence even today in the Indian scenario. More importantly, the history of secondary amenorrhoea along with failed lactation occurring secondary to post-partum haemorrhage is very important since it is a known setting for causation of Sheehan's syndrome (post-partum pituitary necrosis).

Investigations in the present case are outlined in Table 1.

Table 1- Investigations in the present case

Investigation	Result	Reference range for females
Reticulocyte	1.5	0.8–2.0% red cells
WBC count	4.5×10^3	$3.54–9.06 \times 10^3/mm^3$
RBC count	4.95×10^6	$4.00–5.20 \times 10^6/mm^3$
Haemoglobin	11.2	12.0–15.8 g/dL
Haematocrit	35.3	35.4–44.4 %
MCV	82	79–93.3fL
MCH	31.3	26.7–31.9 pg/dL
MCHC	32.1	32.3–35.9 g/dL
Platelet count	241×10^3	$165–415 \times 10^3/mm^3$
ESR	14	0–15 mm at end of 1hr
Fasting Sugar-	78	70-126mg/dL
Post-Prandial	96	140-120mg/dL
Sodium	136	134-146mmol/L
Potassium	4.3	3.6-5.4mmol/L
Urea	23	15-50mg/dL
Creatinine	0.6	0.7-1.5mg/dL
Uric acid	3.4	2.5-7.0mg/dL
Calcium	9.3	9-11mg/dL
Phosphorus	3.4	2.5-5.0mg/dL
Bilrubin (Total)	1.4	0.1-1.2mg/dL
ALT	43	10-60IU/L
AST	32	10-42IU/L
ALP	67	42-121.0 IU/L
Total Protein	7.2	6.0-8.0gm/dL
Albumin	3.8	3.5-5.0gm/dL
Cholesterol	165	150-250mg/dL
Triglycerides	87	20-150mg/dL

Hormonal profile is outlined in table 2.

Table 2- Hormonal profile of the case

Hormones	Result	Reference Value
Free T3	1.65	2.5-3.9pg/ml
Free T4	0.21	0.6-1.12ng/ml
TSH	1.21	0.34-5.6ng/ml
FSH(Follicular)	0.314	1-10IU/ml
LH (Follicular)	1.22	1.68-15.0IU/l
Prolactin	0.34	1.24-8.6IU/l

The hormonal profile shows low T3 and T4 but a normal TSH suggestive of secondary hypothyroidism. FSH and LH are also low. Prolactin is low suggestive of panhypopituitarism. A CT Scan and more preferably an MRI of the pituitary fossa is helpful for visualising the pituitary gland; and also aids to rule out mass lesions of the pituitary.

What is Sheehan's syndrome?

Sheehan's syndrome is one of the few hypopituitarism presentations in which hyperprolactinemia is not a feature unless the infarction occurs within a prolactinoma. Sheehan's syndrome, or necrosis of the pituitary gland, is a rare complication of postpartum haemorrhage initially described in 1937 [1]. The size of the pituitary gland increases 120% to 136% during pregnancy [2-5] because more oestrogen stimulates hyperplasia of lactotrophs during pregnancy [6]. Women with Sheehan's syndrome have varying degrees of hypopituitarism, ranging from panhypopituitarism to only selective pituitary deficiencies [7-9]. The anterior pituitary is more susceptible to damage than the posterior pituitary [10]. Diagnosis of Sheehan's syndrome can be difficult. The diagnosis is based on clinical evidence of hypopituitarism in a woman with a history of a postpartum haemorrhage. Deficiencies of specific anterior pituitary hormones will cause varied symptoms. Corticotropin deficiency can cause weakness, fatigue, hypoglycemia or dizziness. Gonadotropin deficiency will often cause amenorrhoea, oligomenorrhoea, hot flashes or decreased libido. Growth hormone deficiency causes many vague symptoms including fatigue, decreased quality of life, and decreased muscle mass. The most important clue for diagnosis of Sheehan's syndrome is lack of lactation and failure of menstruation resumption after a delivery complicated with severe haemorrhage [11]. Although pituitary gland necrosis is widely accepted mechanism, but other mechanisms are also implicated as the mean age of diagnosis from the index delivery is in years. Moreover, experimental evidence suggests efficient adaptive autoregulation of adenohypophyseal blood flow during hypotension caused by acute blood loss [12,13]. Massive or submassive ischaemic necrosis of the pituitary should result in acute pituitary failure in Sheehan's syndrome akin to that observed in pituitary apoplexy (the latter may be observed in diabetes, sickle cell disease, septic shock, on anticoagulant therapy, etc.) [14]. Tissue necrosis could release sequestered antigens, triggering autoimmunity of the pituitary and delayed hypopituitarism in Sheehan's syndrome [15].

A very close differential diagnosis is "Lymphocytic hypophysitis". In cases of lymphocytic hypophysitis, hyperprolactinemia is expected during pregnancy and during the early postpartum period, and the mass effect of the infiltrate can also contribute to stalk compression and secondary hyperprolactinemia [16].

Sheehan's syndrome is associated with increased all cause mortality, weight loss, menstrual irregularities, low blood pressure, high serum cholesterol levels and acute adrenal crises during stress and infection.

What are the causes of failed lactation?

The causes of failed lactation are outlined in table 3 [17].

What is other name of delayed ankle reflex? Enumerate its causes?

Delayed ankle reflex is called as Woltman's sign. Woltman sign is named after the neurologist William Henry Woltman (1899-1966) who classically described a delay in the relaxation phase of ankle reflex. Delayed ankle reflex is said to be present when it is prolonged more than 320 ms. Delayed ankle reflex is classically described in hypothyroidism (other causes are enumerated in table 4 [18]).

Table 3- Causes of failed lactation are

1. Electromagnetic, Trauma, Radiation Causes
   - Breast irradiation
2. Surgical, Procedure Complication
   - Hypophysectomy
3. Infected organ, Abscesses
   - Mastitis, puerperal
4. Neoplastic Disorders
   - Toxic thyroid adenoma/autonomous
   - Pituitary tumor autolysis/involution
5. Allergic, Collagen, Auto-Immune Disorders
   - Thyroiditis, postpartum type
   - Hypophysitis, autoimmune
6. Relational, Mental, Psychiatric Disorders
   - Anxiety Disorder
7. Arteriosclerotic, Vascular, Venous Disorders
   - Postpartum pituitary Necrosis
8. Vegetative, Autonomic, Endocrine Disorders
   - Hyperthyroid status
   - Hyperthyroidism (Grave's disease)
   - Pituitary disorders
   - Panhypopituitarism
9. Drugs
   - Oral contraceptive administration/Toxicity
   - Estrogen (Premarin/Estinyl) administration/Toxicity
10. Poisoning (Specific Agent)
11. Tobacco smoking/excess

Table 4- Other causes of prolonged reflex relaxation

1. Anorexia nervosa
2. Advanced age
3. Diabetes mellitus
4. Drugs- Beta-blockers, IV dextrose, IV potassium, quinidine, reserpine
5. Hypothermia
6. Peripheral arterial disease
7. Pedal oedema
8. Pregnancy
9. Sarcoidosis

How will you manage a case of Sheehan's syndrome?

A case of Sheehan syndrome requires life long hormone replacement therapy. The order of hormone replacement is same as that of hypopituitarism due to other causes. Corticosteroid is added first- prednisone in the dose of 7.5 mg, 5 mg at morning and 2.5 mg in evening [19]. This should be followed by addition of thyroxine (0.075-0.15 mg/day). Corticosteroid is replaced first because thyroxine therapy can exacerbate glucocorticoid deficiency and theoretically induce an adrenal crisis [20,21]. Conjugated estrogen (0.65-1.25 mg/day) for 25 days and progesterone (5-10mg) on days 16 to 25 is usually started on 7th day. For fertility menopausal gonadotrophins, human chorionic gonadotrophin can be given [19]. Growth Hormone replacement therapy in patients with Sheehan's syndrome may have beneficial effects on quality of life, body composition and lipid profile [22]. Somatotrophin in the dose 0.1-1.25 mg/day is usually given. Vasopressin may be added if required (5-20 mcg twice daily).

How will you monitor thyroid function in this patient?

As the patient is having hypothyroidism secondary to pituitary cause that is secondary hypothyroidism, thyroid function is monitored by measuring free T4 level. The serum TSH levels can be low or normal, usually never high. Unlike primary hypothyroidism serum TSH level is not used for monitoring the effectiveness of thyroxine replacement [23].

Although Sheehan syndrome is uncommon as a result of improved obstetric care, it should be a consideration in any woman who has a history of a postpartum haemorrhage and presents with history of lactational failure, secondary amenorrhoea and signs/symptoms of pituitary deficiency.

Key Points

- Sheehan's syndrome is a rare complication of post-partum haemorrhage.
- Although Sheehan's syndrome is a pregnancy related complication, notably it presents late (mean duration of diagnosis from onset of disease is 5-8 years) as panhypopituitarism.
- Lactational failure and secondary amenorrhoea are the hallmarks which should prompt for diagnosis of Sheehan's syndrome.

Conflict of interest: None declared.

Source of funding: Nil.

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