

ENDOCRINE DYSFUNCTIONS IN TUBERCULOSIS

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INTRODUCTION

Tuberculosis (TB) is considered one of the common illnesses in developing countries and is known to affect all classes of society. Though the subclinical endocrine dysfunction is common in subjects with tuberculosis, overt manifestations are very rare. The incidence of endocrine involvement in tuberculosis was high in the pre-antibiotic era but it has reduced to a large extent in the recent years [1]. However, it is advisable to keep vigil and high degree of suspicion for early diagnosis of endocrine dysfunction, as some of the deficiencies like adrenal dysfunction can lead to serious consequences. Also, there are diagnostic difficulties in subjects who are already on antitubercular therapy [ATT] due to several drug interactions affecting the peptide and steroid metabolism. For example, treatment of primary endocrine deficiency with glucocorticoids for adrenal insufficiency is known to predispose or reactive old foci of tuberculosis. Table 1 depicts guidelines for suspecting endocrine dysfunction in cases of pulmonary tuberculosis. Table 2 shows the effects of ATT on the endocrine system.

Table 1 : Guidelines for suspecting endocrinological dysfunction in case of tuberculosis and the confirmatory tests

- 1. Thyroid dysfunction:**
Painless/painful thyromegaly with or without lymphadenopathy
Solitary node/ Multi nodular goitre / Mass lesion (FNAC required)
Sick euthyroid syndrome
Confirmatory test: FNAC
- 2. Adrenal dysfunction :**
Hypotension, Hyperpigmentation, Salt craving, More evident after initiating ATT, Confirmatory tests: ACTH stimulation test
CT adrenals with or without FNAC
- 3. Gonadal dysfunction :**
Persistently reduced libido after resolution of Constitutional symptoms
Thickening of vas defrens
Prolonged amenorrhoea
Unresponsive to progesterone withdrawal/E+P (endometritis)
Confirmatory test :FNAC/biopsy

4. Pituitary dysfunction:

Growth retardation (following TB meningitis)
Hyponatremia without edema (SIADH)
Polyuria, polydipsia (diabetes insipidus)
Confirmatory test : Clonidine/Insulin tolerance test
For GH insufficiency
Plasma osmolality and urinary osmolality
For SIADH
Dehydration test for diabetes insipidus

5. Calcium metabolism:

Polyuria, Pruritus, Hypercalcemia, Hypercalciuria,
Confirmatory test : Serum 1,25, (OH)₂ D3 levels,
Serum calcium, urinary calcium excretion

6. Diabetes and pancreatic dysfunction:

Atypical presentation of tuberculosis
Abdominal mass with or without ascites
Confirmatory test: CT scan/USG abdomen
FNAC/biopsy

ADRENAL DYSFUNCTION

Tuberculosis is known to affect adrenal glands directly. Adrenal destruction by tuberculosis may lead to overt or subclinical adrenal insufficiency, and it continues to be the most common cause of Addison's disease in India [2]. However in the West, tubercular adrenalitis uncommon, and the incidence was between 0-55% in various series. Though basal cortisol level was low in a significant number of patients, cortisol was normal after ACTH stimulation [3]. Enlargement of adrenal gland has also been described in patients with active tuberculosis, albeit with normal adrenal reserves [4].

The low dose ACTH stimulation test using 1 mcg of ACTH was described for diagnosis of subclinical adrenal dysfunction (5). CT scan of abdomen in cases of tubercular adrenalitis shows typical features of shrunken and calcified adrenals in chronic stage and enlarged in the active stage [4,6]. FNAC of the adrenals may be used to confirm the diagnosis of tubercular adrenalitis in acute cases as they may of ten present with enlarged adrenals.

The anti-tubercular drugs are known to increase the degradation of corticosteroids. Initiation of anti-tubercular therapy may lead to overt manifestations

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of Addison's disease in cases with already existing subclinical adrenocortical insufficiency. Addisonian crisis has also been reported with the initiation of rifampicin therapy [7,8].

Table 2 : Effect of ATT on endocrine system

1. Thyroid:	TBG rises (with rifampicin, INH, pyrazinamide) T3RU decreases Goiterogenic (with PAS)
2. Adrenal:	Increases steroid metabolism Precipitates Addisonian crisis
3. Gonads:	Failure of oral contraceptives
4. Calcium metabolism	Masks hypercalcemia and hypercalciuria
5. Diabetes:	Causes insulin resistance Increases insulin requirement Accelerates OHA metabolism

Subjects with tuberculosis who are already on corticosteroid replacement therapy may need to increase the steroid dose following ATT. Diagnostic evaluation of adrenal reserve in subjects on ATT is very difficult due to abnormal steroid metabolism[9].

Reversal of adrenal function following anti-tubercular therapy is a controversial issue. Some of the studies have shown that there is normalization of adrenal function following therapy in a large number of cases, while others have contradicted it. [10].

On the other hand, corticosteroid therapy for endocrinal or non-endocrinal indications is also known to increase the incidence of reactivation of old tubercular foci. However, this has been a matter of debate for several years (11). Upto 12% of new cases and 44% of reactivation of genital tuberculosis have been reported in patients started on steroid therapy [12].

Studies have suggested that glucocorticosteroid hormones used in combination with tuberculostatics accelerated the fading of the exudative phase of tuberculous inflammation and that steroid use during the early stages of the treatment increased healing in the lungs. However, 10 to 15 days after

the start of their use, immunosuppressive action on T-lymphocytes was detected.

Steroid hormones had the most pronounced suppressive effect on lymphocyte blast cell transformation with mitogens persisting even after discontinuation of their use (13). Corticosteroids have shown weak effects of gamma interferon and 1,25 di-hydroxy vitamin D levels in tuberculosis and the net effect on monocytes was to decrease immunity against tuberculosis [14].

Catecholamine levels were increased significantly with the severity of the disease suggesting that the stress of infection plays a role in induction of enzymes responsible for catecholamine synthesis with subsequent stimulation of ACTH and cortisol synthesis [15].

THYROID DYSFUNCTION

Thyroid gland is rarely involved directly by tubercle bacilli. The first case of thyroid involvement in tuberculosis was reported in late 1800s. In pre-antibiotic era, the incidence was as high as 14% in autopsy series (1). However in post-antibiotic era, only a few cases were reported. The estimated prevalence rate was approximately 1.15% diagnosed on FNAC with female preponderance, as male to female ratio was 1:2 [16]. The spread of mycobacteria to the thyroid gland is either through haematogenous route or from adjacent foci.

Diagnosis of tuberculosis thyroiditis was rarely made clinically because of its mild presenting features and rarity of disorder. As most patients usually present with symptoms of thyroid enlargement or nodule and constitutional symptoms such as weight loss, the first possible diagnosis considered is malignancy of thyroid. Tuberculosis usually presents with painless thyroid nodule and lymphadenopathy. However, it may also present with a thyroid mass, thyroiditis (painful swelling) or as an acute or cold abscess with or without a discharging sinus [17].

A few cases of thyroid involvement have also been reported in association with miliary tuberculosis papillary carcinoma of thyroid and tuberculosis of thyroid bed presenting later as recurrent medullary thyroid carcinoma [18,19]. Tuberculous adenitis of thyroid has been reported to mimic subacute thyroiditis. Local spread from lymph nodes to the thyroid gland has also been well described. However, some case reports suggested that paravertebral abscess might spread to thyroid region

and mimic as carcinoma of thyroid with a paravertebral swelling [20]. In older series, cases were diagnosed on autopsy but now FNAC is a sensitive tool for the diagnosis of tuberculosis of thyroid [16].

Functional disorders of thyroid has been rarely reported, and tuberculosis might manifest as thyrotoxicosis or hypothyroidism [21,22,23]. Sick euthyroid syndrome was reported frequently in subjects with tuberculosis, and its prevalence has been described in upto 92% of subjects in one of the series [3]. About 60% of subjects were reported to have low triiodothyronine (T3) level or elevated tetraiodothyronine (T4) to T3 ratio [24]. Thyroid dysfunction has described more commonly in subjects who have diabetes along with tuberculosis. Serum T3 levels in sick euthyroid syndrome predicted mortality, as free T3 concentration at presentation in sick euthyroid patients who dies, was significantly lower than in those who survived ($P < 0.05$). Undetectable free T3 concentration at presentation was associated with a subsequent mortality in about 75% of the subjects [25].

Anti-tubercular therapy (ATT like INH, rifampicin, ethambutol and/or pyrazinamide) was known to affect the thyroid function. Thyroid binding globulin (TBG) is shown to rise following initiation of ATT and T3RU decreases. However, some of the reports have also shown subnormal T3 in as much as 61% of TB patients, While T4, thyrotropin (TSH) and TBG were normal [26]. Due to alteration in binding proteins, the features of thyrotoxicosis did not manifest in a case of toxic thyroid adenoma, as T3 and T4 were low due to anti-tubercular therapy [27].

GONADAL DYSFUNCTION AND INFERTILITY

Tuberculosis is one of the important causes for endometritis causing infertility in young females. Endometrial biopsy and the culture of AFB from the biopsy material may help in the diagnosis of the genital tuberculosis [28]. Studies have also shown higher incidence of associated gonadal dysfunction in upto 56% patients of genital tuberculosis [29].

Males are less commonly involved due to tubercular epididymo-orchitis. One study has shown that 72% of subjects with active tuberculosis had hypogonadotropic hypogonadism [3] and tuberculous meningitis involving hypothalamo-pituitary stalk was one of the important causes of hypogonadotropic hypogonadism [30].

Anti-tubercular drugs are known to affect the metabolism of sex hormones. In one study during treatment with ATT, there was a moderate, but significant increases in plasma estradiol and estrone, while plasma estrone sulfate was significantly reduced. Plasma testosterone was unaltered, but there was a slight (mean 15%) increase in plasma androstenedione. Of all the anti-tubercular drugs, rifampicin was more frequently blamed for alteration in steroid hormone metabolism [31]. Such interaction in those who are taking oral contraceptives may cause increased steroid degradation and lead to contraceptive failure.

ANTERIOR PITUITARY DYSFUNCTION

Pituitary involvement was observed in 4% of patients with tuberculosis in the preantibiotic era [1], and the route of spread was haematogenous or local extension from sphenoid sinus, brain, or meninges. The affected patient may present with fever, headache and ophthalmopathy. Hypopituitarism has been documented in 20% of patients, years after recovery from tuberculous meningitis in childhood. The cause appeared to be tuberculous lesions affecting the hypothalamus, pituitary stalk and directly or indirectly, the pituitary itself [32].

Growth hormone (GH) is known to cause immunomodulation through superoxide production, induction of macrophage activation factor and activation of monocytes. But GH does not induce tumour necrosis factor and thus it has no effect on monocyte cell adherence to mycobacteria [33].

CIRCADIAN RHYTHM

Patients with tuberculosis exhibit impairment of the circadian cycle of the hormones with acrophase in the day and evening hours (4-8 pm), reduced mean levels and amplitude of fluctuation and non-coincidence in time. The derangement in the rhythm was more distinct in disseminated tuberculosis with intoxication symptoms [34].

ADOLESCENCE

The initial period of the tuberculous infection in adolescents is marked by the following changes: inhibited pituitary (other than adrenocorticotropic hormone), higher adrenal activity, elevated cortisol levels, altered (predominantly depressed) thyroidal function and increased pancreatic functional activity [35].

DIABETES INSIPIDUS AND SIADH

Diabetes insipidus (DI) manifests more often in children following tubercular meningitis than in adults. It may also occur as a part of panhypopituitarism if the intrasellar pathology interrupts the hypothalamopituitary pathways or its suprasellar extensions. As the hypothalamopituitary pathways are in close proximity to the basal cistern and they are the most affected in tuberculous meningitis, DI is more common in tuberculosis [36].

Syndrome of the inappropriate ADH secretion (SIADH) is more commonly seen in children with tuberculosis and there are several causative factors for SIADH in tuberculosis. Tubercular chest lesion, as well as tubercular meningitis may be followed by SIADH. Upto 60% of the patients with tubercular meningitis may present with SIADH or hyponatremia at initial presentation [37], and atrial natriuretic peptide was high in these subjects with hyponatremia [38]. SIADH is usually reversible with effective treatment of tuberculosis in most cases [37]. Subjects with tuberculous meningitis and SIADH were also known to have higher intracranial pressure when compared to those without SIADH [39]. Water overload with hyponatremia associated with active tuberculosis has been explained as due to downsetting of osmoregulation induced by active tuberculosis (reset osmostat) [40].

DYSFUNCTION OF PARATHYROIDS AND MINERAL METABOLISM

In granulomatous diseases, disturbances in calcium metabolism due to excess production of 1,25-dihydroxy vitamin D₃ have been described. Hypercalcemia in patients with tuberculosis was generally due to hypervitaminosis D [41], but some studies have also shown that it was independent of calcitriol levels. The calcitropic hormone study in untreated active pulmonary tuberculosis (PTB) among Hong Kong Chinese, demonstrated higher albumin adjusted serum calcium despite a lower calcium intake. There was no significant change in serum 25 (OH) D or 1,25 (OH)₂ D₃ concentrations and serum parathyroid hormone was significantly lower in these patients with PTB [42].

Subjects with PTB with low 1,25 (OH)₂ D₃ and low parathormone (PTH) also had hypercalcaemia which subsided spontaneously [43]. In a few subjects with PTB, hypercalcemia was not marked due to associated vitamin D deficiency, but it was unmasked after they had adequate exposure to sunlight [44].

Levels of 1,25 (OH)₂ vitamin D₃ were higher in pleural fluid than in the serum of tuberculosis patients and this gradient was significant [45]. The immunomodulatory effect of 1,25 (OH)₂ D₃ was well recognized and its natural protective effect on macrophages altered the course of disease [46]. Invitro studies using pyrazinamide and 1,25 (OH)₂ D₃ have shown that they act synergistically on tuberculosis bacilli through modulation of macrophages [47].

Absorptive hypercalciuria is a frequent finding in upto 25% patients with tuberculosis. Studies with high and low calcium diets showed that there was persistent hypercalciuria in tuberculosis, low calcidiol level and higher calcitriol level when compared to controls [48]. Therapy with ketoconazole reduced serum calcitriol levels and the serum calcium levels [49], and hypercalciuria also subsided following anti-tubercular therapy [50].

Antituberculous chemotherapy agents particularly rifampicin and isoniazid, affect vitamin D metabolism. During therapy, serum ionized calcium and 24-hour urine calcium excretion were normal but plasma PTH rose to higher levels. Following completion of chemo-therapy, hypercalcemia and hypercalciuria returned to levels similar to those observed pre treatment. Serum 25-hydroxyvitamin D was low at 6.25 nmol/l (normal 20 to 90 nmol/l) during antituberculous chemotherapy, but was normal before and after [51]. Both rifampicin and isoniazid are known to cause bio-chemical evidence of vitamin D deficiency, which induces a state of resistance to parathyroid hormone thereby masking the hyperparathyroidism and hypercalcaemia until the chemotherapy is completed (51).

TUBERCULOSIS AND PANCREAS

Although tuberculosis of gastrointestinal tract is common, tuberculosis of pancreas is rarely reported [52]. Usually these patients present with an abdominal mass and the common differential diagnosis is from other mass lesion or abscess [53,54,55]. On biopsy or aspiration the diagnosis of tuberculosis is usually confirmed. Wsome patients are asymptomatic while others may present with obstructive jaundice, pain or gastrointestinal bleed.

TUBERCULOSIS AND DIABETES MELLITUS

Diabetes mellitus (DM) and tuberculosis were considered as the major killers in the olden days. In one review of tuberculosis and diabetes in 1934 by Root, it was stated that ‘... during the later half of 19th century the diabetic patient appeared doomed to

die of pulmonary tuberculosis, if he succeeds in escaping coma....’.

Autopsy series in 1800's found the incidence of tuberculosis ranged from 38% to more than 50% in subjects with diabetes [1]. However, in the later series, it was found that the incidence of pulmonary tuberculosis in diabetics was 10 times more than that in non-diabetics [56]. Even as large a number as 85% of the subjects after the onset of DM, were known to suffer from TB [57].

The higher incidence of PTB in subjects with DM is presumed due to defective defensive mechanisms. These subjects have impairment of leukocytes and lymphocyte-mediated responses to infection and impairment of macrophage functions. Tuberculous infection in diabetes was usually due to reactivation of old focus rather through fresh contracts [58]. Diabetics have an atypical clinical presentation in the form of higher incidence of cavitory lesions and sputum positivity, mild or absent toxic symptoms, involvement of lower lobes and more severe involvement [59,60]. There was no evidence that treatment of active tuberculosis in diabetics was less effective than in non diabetics. INH prophylaxis in subjects with positive tuberculin test and negative X-ray chest was debated [61,62] and is not generally accepted.

ATT interacts adversely with oral anti-diabetic therapy. Rifampicin may accelerates the metabolism of oral hypoglycemic agents. INH has antagonistic action on sulphonylureas. Thus, in diabetic subjects with tuberculosis, weight loss, appetite and severe intercurrent illness are the indications for insulin therapy.

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