

Pituitary Hormone Involvement in Tuberculous Meningitis

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Background and study aim: Hypopituitarism has been reported in about 20% of patients, even years after recovery from tuberculous meningitis (TBM) in childhood. Pituitary involvement is a significant complication of TBM and clinicians should be aware of the potential involvement of the pituitary gland in TBM cases. The study aimed to determine changes in pituitary hormone levels in newly diagnosed TBM cases.

Patients and Methods: A cross-sectional, observational study, included all adult admitted cases diagnosed as TBM based on Ahuja criteria. Clinical features of the included cases were noted. Analysis of CSF and pituitary hormone levels, imaging like CT scan brain and where possible MRI were done. Data was statistically analysed.

Results: Out of the 40 TBM cases, 2 were definite cases with CSF CBNAAT being positive, 10 were highly probable and rest 28 were probable as per modified Ahuja criteria. Lumbar puncture was done in all

cases and CSF analysed. CSF analysis showed > 20 cells in 35 cases and for all such cases CSF protein was raised, sugar was low. 38 TBM cases had suggestive neuroimaging, where basal exudates and gyral enhancement were the most common radiological abnormality noticed. More than one hormone disbalance was noted in 9 cases. Serum cortisol and ACTH was low in 20% cases, while serum prolactin was high in 7.5% cases. SIADH was diagnosed in 15% cases. Testosterone was low in 3.7% males and FSH was low in 15.3% females. TSH and free T4 was low in 15% and 12.5% patients respectively. IGF-1 was low in only 5% patients. The involvement of pituitary hormones in TBM is not directly related to the disease itself but can occur as a consequence of the infection.

Conclusion: The specific impact on pituitary hormone function can vary depending on the severity and duration of the infection, as well as individual factors.

INTRODUCTION

Tuberculosis (TB) is one of the commonest infectious diseases in developing countries like India. TB, caused by the bacteria *Mycobacterium tuberculosis*, is known to affect almost every organ of our body except hair, nail and enamel. Endocrine involvement in TB is a distinct entity with high incidence in the pre-antibiotic era. However, although the incidence has reduced now with usage of anti-mycobacterial drugs, still it remains an important clinical entity with post infection sequelae [1]. Hypopituitarism has been reported in

about 20% of patients, even years after recovery from tuberculous meningitis (TBM) in childhood. Tuberculous lesions affect the hypothalamus, pituitary stalk and directly or indirectly, the pituitary itself [2]. The route of spread includes hematogenous and local extension from brain, meninges or sphenoid sinus [1]. Apart from anterior pituitary endocrinal dysfunction, TBM also manifests as diabetes insipidus and syndrome of inappropriate ADH secretion (SIADH). Diabetes insipidus is more common in children as compared to adults. It can occur as

part of panhypopituitarism [3]. It is reported that up to 60% of patients with TBM may present with SIADH or hyponatremia at initial presentation and it is usually reversible with treatment of TB in most cases [4]. Thus, pituitary involvement is an important complication of TBM and clinicians should therefore be aware of this entity.

METHODS

The study had a cross-sectional, observational design and was carried out for a period of one year in the inpatient department of a tropical disease institute in India. The study included all cases of 18 to 60 years age of either sex admitted in indoor newly diagnosed as TBM based on Ahuja criteria. Other meningitis due to infective aetiologies were excluded. Those receiving glucocorticoids more than 3 weeks or diagnosed endocrine illnesses or on hormone therapy including oral contraceptives, levothyroxine was excluded. HIV seropositive patients, pregnant or lactating mothers were excluded from the study.

Clinical features of the included cases were noted. Cerebrospinal fluid (CSF) analysis was performed. Pituitary hormone levels were measured using electron chemiluminescent immunoassay. Wherever possible, imaging like Computerized Tomography (CT) scan brain and Magnetic Resonance Imaging (MRI) were done. TBM cases were diagnosed using Ahuja criteria [5] which included Clinical, radiological and laboratory parameters, as follows:

a) Clinical

Fever and headache lasting for more than 14 days (mandatory). Vomiting, alteration of sensorium or focal deficit (optional).

b) Cerebrospinal fluid

Pleocytosis with more than 20 cells, predominantly (greater than 60%) lymphocytes, protein greater than 100 mg%, sugars less than 60% of corresponding blood sugars. Negative India ink studies and cytology for malignant cells (in relevant situations).

c) Radiological

CT studies of the head showing 2 or more of the following:

1. Exudates in basal cisterns or in Sylvian fissures

2. Hydrocephalus
 3. Infarcts
 4. Gyral enhancement.
- d) Extra neural TB

Active TB of lungs, gastrointestinal tract, urogenital tract, lymph nodes, skeletal system or skin as evidenced by appropriate radiological or microbiological tests or by the presence of caseation necrosis on histopathological examination.

Based on the above criteria, patients are categorized into:

1. Definite tuberculous meningitis
 - i. Clinical criteria (A)
 - ii. Bacterial isolation from CSF or diagnosis at autopsy
2. Highly probable tuberculous meningitis
 - i. Clinical criteria (A)
 - ii. All 3 of (B) and (C) and (D)
3. Probable tuberculous meningitis
 - i. Clinical criteria (A)
 - ii. Any 2 of B, C and D
4. Possible tuberculous meningitis
 - i. Clinical criteria (A)
 - ii. Any one of (B) (C) and (D)

SIADH was diagnosed using Schwartz and Bartter Clinical Criterion [6] which includes:

- i. Serum sodium less than 135mEq/L
- ii. Serum osmolality less than 275 mOsm/kg
- iii. Urine sodium greater than 40 mEq/L (due to ADH-mediated free water absorption from renal collecting tubules)
- iv. Urine osmolality greater than 100 mOsm/kg
- v. Absence of clinical evidence of volume depletion - normal skin turgor, blood pressure within the reference range
- vi. Absence of other causes of hyponatremia - adrenal insufficiency, hypothyroidism, cardiac failure, pituitary insufficiency, renal disease with salt wastage, hepatic disease, drugs that impair renal water excretion.
- vii. Correction of hyponatremia by fluid restriction

Tests for SIADH included serum osmolality and serum sodium, urine sodium concentration and osmolality, renal function tests, random blood sugar, thyroid profile, serum cortisol, serum electrolytes, fasting lipid profile and liver function tests.

Data collected was statistically analysed. Descriptive data was represented as mean, standard deviation, frequency or percentages, as applicable. Different levels were expressed at 95% Confidence Interval. All Statistical analysis for various measures was performed using various standard statistical software packages like Microsoft Excel and GraphPad Prism.

RESULTS

Out of the 40 TBM cases, 27 were males and 13 females. Categorizing TBM, 2 were definite cases with CSF CBNAAT being positive. 10 were highly probable cases, i.e., they met clinical criteria, CSF criteria, radiological criteria and had extra neural involvement. Rest 28 cases were probable as per modified Ahuja criteria, i.e., they had clinical features suggestive of TBM along with any 2 of CSF, radiological and extra neural involvement criteria. Mean age was 31.8 years. All cases were anaemic. (Table 1). Hypotension (BP<100/60 mmHg) was noted in 30% cases; hypoglycaemia (<70mg/dl) in 20% cases and hyponatremia (Serum Na⁺ <135 meq/L) was seen in 70% cases.

All cases presented with fever and headache, while altered sensorium was noted in 80% cases. Vomiting was noted in 8 cases. 3 cases had Focal neurological deficit and 2 had seizures. Lumbar puncture was done in all cases and CSF

analysed. CSF analysis showed > 20 cells in 35 cases, where CSF protein was raised - >100mg%, sugar was low (<60% of blood sugar at same time). In 5 cases, CSF was not suggestive. India ink stains of CSF were negative in all cases. CSF CBNAAT was positive in only 2 cases. CSF for AFB stain was negative in all cases. ADA of CSF was high in 18 cases. 38 TBM cases had suggestive neuroimaging. 38 cases had ≥2 of radiological criteria - basal exudates, infarct, hydrocephalus and gyral enhancement. Basal exudates and gyral enhancement were the most common radiological abnormality noticed. (Figure 1)

12 cases had other sites of TB involvement- pulmonary TB in 1 case. 12 had lymphadenopathy – cervical and/ or axillary. 8 had retroperitoneal lymph nodes in USG whole abdomen. CT abdomen for adrenal gland was normal in all patients.

More than one hormone disbalance was noted in 9 cases. Serum cortisol and ACTH was low in 20% cases, while serum prolactin was high in 7.5% cases. SIADH was diagnosed in 15% cases. Testosterone was low in 3.7% males and FSH was low in 15.3% females. TSH and free T4 was low in 15% and 12.5% patients respectively. IGF-1 was low in only 5% patients. (Table 2)

Follow up was done up to after 1year of treatment completion in all cases. More than one year couldn't be done in all cases as some cases were lost to follow up. At 1year follow up, repeat test of hormones revealed reversal to normal levels except for IGF 1, which still remained low, although it's level increased.

Table (1): Characteristics of TBM Cases.

Patient Characteristics	Observations
Age (in years) [Mean ± SD]	31.8 ± 8.24
Sex ratio (M: F)	27:13
Hemoglobin (g/dl) [Mean ± SD]	10.57 ± 0.96
Total Leukocyte Count (10 ⁹ /l) [Mean ± SD]	7761.68 ± 1210.51
Hypotension [n (%)]	12(30%)
Hypoglycaemia [n (%)]	8 (20%)
Hyponatremia [n (%)]	28(70%)

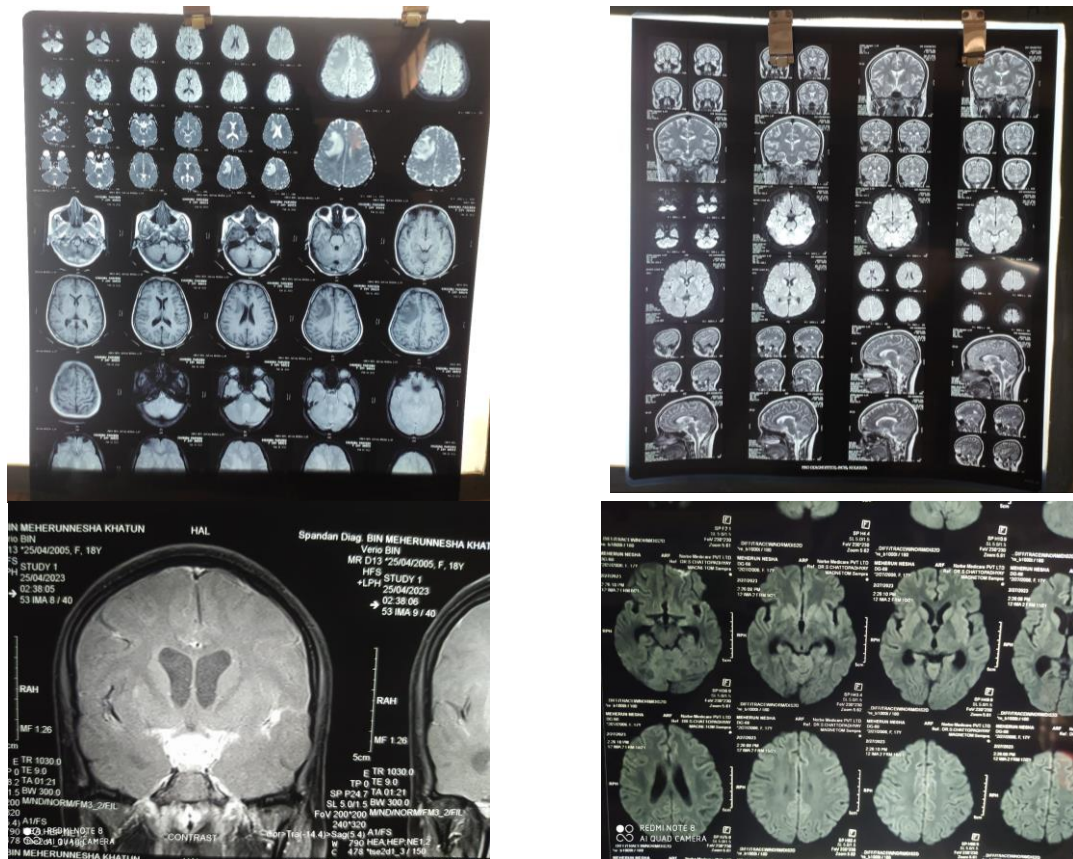


Figure 1: MRI Brain of TBM cases showing basal exudates, infarction, granuloma

Table (2): Hormonal Profile of TBM Cases

Hormonal Profile of TBM cases		
Hormone	Levels	No of cases (n=40)
Serum cortisol	Normal (10 – 25 microgm/dl morning sample)	32
	Low	8
Serum ACTH	Normal (10 to 40 pg/ml early morning sample)	32
	Low	8
Serum Prolactin	Normal (<25 ng/ml in nonpregnant female and <20 ng/ml in males)	37
	High	3
FSH	Normal (4.7-21.5IU/L for menstruating females)	11
	Low	2
TSH	Normal (0.5 – 5 mIU/L)	34
	Low	6
Free T4	Normal (0.8-1.8ng/dl)	35
	Low	5
IGF-1	Normal (12 – 20years: 127-896ng/ml; 81 – 358 ng/ml in adults > 20 years – 40years)	38
	Low	2
Testosterone	Normal (160 to 728ng/dl in 20 -49 years male)	26
	Low	1
ADH	SIADH absent	34
	SIADH diagnosed	6

Note:
 TBM= Tuberculous Meningitis; ACTH= Adrenocorticotropic Hormone; FSH= Follicle-stimulating hormone; TSH= Thyroid-stimulating hormone; IGF= Insulin-like growth factor; ADH= Anti-diuretic hormone; SIADH= Syndrome of Inappropriate ADH Secretion

DISCUSSION

The involvement of pituitary hormones in TBM is not directly related to the disease itself but can occur as a consequence of the infection. TBM can cause inflammation and damage to the hypothalamus and pituitary gland and play a crucial role in regulating hormone production and release. The specific impact on pituitary hormone function can vary depending on the severity and duration of the infection, as well as individual factors [7].

One of the most common endocrine abnormalities associated with TBM is diabetes insipidus. It occurs due to the damage to the hypothalamus or pituitary gland, resulting in a deficiency of antidiuretic hormone (ADH), also known as vasopressin. ADH helps regulate the balance of water in the body, and its deficiency leads to excessive thirst and increased urine production. TBM can also cause damage to the pituitary glands' corticotroph cells, which produce adrenocorticotrophic hormone (ACTH). ACTH stimulates the adrenal glands to produce cortisol, a hormone essential for stress response and metabolism. In cases where the pituitary gland is affected, adrenal insufficiency can occur, leading to low cortisol levels and potentially causing symptoms such as fatigue, weakness, and weight loss. The pituitary gland also produces growth hormone (GH), which plays a vital role in growth, metabolism, and body composition. In some cases of TBM, damage to the pituitary gland can result in growth hormone deficiency, leading to growth retardation in children and potentially affecting metabolism in adults [7].

Aristotelis T et al. studied 16 patients admitted with infectious meningitis. They reported 5 patients (31.25%) to have apparent pituitary hormone deficiencies. Two had gonadotropic and three had somatotrophic hormone deficiency [7]. In our study, we found Serum cortisol and ACTH to be low in 20% cases, while serum prolactin was high in 7.5% cases. SIADH was diagnosed in 15% cases. Testosterone was low in 3.7% males and FSH was low in 15.3% females.

A study by Dhanwal et al. included 75 TBM cases. They reported 42.7% cases to have relative or absolute cortisol insufficiency. 30.7% cases had central hypothyroidism and 49.3% cases had hyperprolactinemia. 29.3% cases had multiple hormone deficiencies [8]. TSH and free T4 was low in 15% and 12.5% patients

respectively in our study. A study by Lam et al., involving 49 cases, reported 10 patients to have abnormal pituitary function. 7 of them had growth hormone deficiency [2]. 4 of them also had gonadotropin deficiency [9]. More than one hormone disbalance was noted in 9 cases in our study.

Three large case series reported hyponatremia as a common electrolyte abnormality in patients with active TB, with incidences varying from 11% to 51% [9,10,11]. Our study could diagnose SIADH in 15% cases. Association of pulmonary TB with SIADH was first reported by Weiss and Katz [12], who reported excess urinary sodium excretion in four patients with active pulmonary TB and hyponatremia. With marked fluid restriction, the patients had an increase in the serum sodium and decrease in urinary sodium excretion, and all surviving patients had normalization of their serum sodium levels during anti-TB therapy [12]. Various mechanisms have been suggested for the development of SIADH in patients with pulmonary TB. One mechanism suggests that hypoxemia associated with pulmonary TB may lead to baroreceptor stimulation, leading to arginine vasopressin release from the posterior pituitary gland [13]. A shift in osmoregulation during active TB has also been suggested as another mechanism. A study by Hill et al. measured arginine vasopressin levels in patients with pulmonary TB, where the levels were elevated despite presence of hyponatremia and subsequently declined after the administration of free water. Such response to a hypo-osmolar stimulus suggests that osmoregulation was functioning but at a lower set point for serum osmolality [14]. Another mechanism highlighted stresses on ectopic production of arginine vasopressin [15].

Pituitary insufficiency is commonly attributed to conditions like pituitary adenoma, craniopharyngioma, Sheehan's syndrome, lymphocytic hypophysitis, irradiation, surgery, or CNS infections [16]. There has been reports of hypopituitarism following snake bite [17]. In a child with tubercular meningitis, precocious puberty has been observed [18]. Pituitary dysfunction in form of short stature, hypogonadism, adrenal deficiency and hyperprolactinemia in 20% of patients after childhood TBM has been reported [2]. TB also appears to be an important, often overlooked

cause as reported by various studies and also as found in our cases.

The study has its limitation in being a small sample study with cross-sectional design. Long term follow up could not be done to see for residual hormonal changes and their effects. Moreover, MRI brain with focus on pituitary, couldn't be done in all cases - so, some important radiological finding might have been missed. Also, histopathological changes in the pituitary gland in TBM cases could not be evaluated. Further research should overcome these limitations.

CONCLUSION

TBM patients should undergo pituitary hormone profile and they should also be followed up in order to avoid any long-term hormonal affection sequelae. Early recognition and treatment are beneficial to prevent such sequelae.

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Conflict of Interest: None Declared.

Ethical Considerations:

The study and its procedures were duly approved by the Institutional Ethics Committee vide approval no CREC-STM/338, and written consent was obtained from all the study subjects' caregiver prior their participation.

HIGHLIGHTS

1. Itself but can occur as a consequence of the infection. The specific impact on pituitary hormone function can vary depending on the severity and duration of the infection, as well as individual factors .
2. Pituitary involvement is an important complication of TBM and clinicians should therefore be aware of this entity .
3. Early recognition and treatment are beneficial to prevent sequelae.

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