

Hypothalamic pituitary dysfunction in acute nonmycobacterial infections of central nervous system

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ABSTRACT

Background and Objective: Acute and chronic central nervous system (CNS) infections are not uncommon in tropical countries and are associated with high morbidity and mortality if specific targeted therapy is not instituted in time. Effects of tubercular meningitis, a form of chronic meningitis on hypothalamic pituitary axis, are well known both at the time of diagnosis and after few months to years of illness. However, there are few reports of pituitary dysfunction in subjects with acute CNS infections. Therefore, this study was aimed at evaluating the pituitary hormonal profile in patients with nonmycobacterial acute meningitis at the time of presentation.

Materials and Methods: This prospective case series study included 30 untreated adult patients with acute meningitis, meningoencephalitis, or encephalitis, due to various nonmycobacterial agents, admitted and registered with Lok Nayak Hospital, Maulana Azad Medical College, New Delhi, between September 2007 and March 2009. Patients with preexisting endocrine diseases, tubercular meningitis and patients on steroids were carefully excluded from the study. The basal pituitary hormonal profile was measured by the electrochemiluminescence technique for serum cortisol, luteinizing hormone (LH), follicular stimulating hormone (FSH), prolactin (PRL), thyrotropin (TSH), free tri-iodothyronine (fT3), and free thyroxine (fT4). **Results:** The cases ($n = 30$) comprised of patients with acute pyogenic meningitis ($n = 23$), viral meningoencephalitis ($n = 4$), brain abscess ($n = 2$), and cryptococcal meningitis ($n = 1$). The mean age of patients was 28.97 ± 11.306 years. Out of 30 patients, 14 (46.7%) were males and 16 (58.1%) were females. Adrenal insufficiency both absolute and relative was seen in seven (23.3%) and hyperprolactinemia was seen in nine (30.0%) of the patients. One study subject had central hypothyroidism and seven (23.3) showed low levels of LH and/or FSH. None of patients showed clinical features suggestive of central diabetes insipidus. **Conclusion:** Acute infections of the CNS are associated with abnormalities in the pituitary hormone profile. Further studies are required to evaluate the hypothalamic pituitary axis using dynamic tests and imaging by MRI.

Key words: Acute central nervous system infections, hypothalamic pituitary axis, hypothalamic pituitary dysfunction, meningitis, nonmycobacterial CNS infections, pituitary hormones

INTRODUCTION

Hypothalamic–pituitary insufficiency is a common endocrine entity in hospital-based clinical practice. The common causes include pituitary tumors such as adenoma

and craniopharyngioma, Sheehan's syndrome, lymphocytic hypophysitis, irradiation, or surgery.^[1] Infectious diseases of the central nervous system (CNS) may also affect the hypothalamus and/or the pituitary gland. Most common infectious agent affecting the hypothalamic pituitary axis is mycobacterium tuberculosis. In a recent study, we have reported pituitary hormone abnormalities in subjects with tubercular meningitis at the time of diagnosis.^[2] Nonmycobacterial acute CNS infections are a relatively rare cause of hypopituitarism and have been published as isolated case reports and few retrospective studies.^[3-5] Further, there is only one prospective study by Tsiakalos *et al*, who concluded that 31% of such cases have hypothalamic pituitary dysfunction at the time of diagnosis.^[6] A recent

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retrospective study by Schaefer *et al.* had concluded that hypothalamic pituitary dysfunction, especially isolated corticotrophin insufficiency, developed in 21% patients after 10–56 months of infectious diseases of the CNS.^[5] Unrecognized selective or panhypopituitarism as a part of a critical illness is associated with worse overall prognosis, increased risk of severe infectious complications, and reduced survival.^[7] Lack of substantial data on pituitary insufficiency especially from tropical countries in acute CNS infections prompted us to carry out this study.

MATERIALS AND METHODS

This prospective study was conducted in Maulana Azad Medical College and associated Lok Nayak, Govind Ballabh Pant and Guru Nanak Eye Centre Hospitals, a tertiary care referral institute in New Delhi, India, after ethical clearance. The study was conducted according to the Declaration of Helsinki, and the study protocol was reviewed and approved by the institutional ethics committee. This study was parallel work along with hypothalamic pituitary dysfunction in tubercular meningitis which we have been already published.^[2] A written informed consent was taken from each patient prior to inclusion in the study. Study included 30 untreated adult patients presenting with acute pyogenic meningitis, viral meningoencephalitis, and cryptococcal meningitis. Pregnant, post-partum and lactating females, those receiving glucocorticoids for any coexisting illness, those with coexisting endocrine illness with or without any form of hormonal therapy including contraceptives, thyroid hormones and postmenopausal replacement were carefully identified and excluded. A detailed clinical, biochemical, hormonal assessment of each included patient was done and recorded in a preset proforma. All study subjects were evaluated for serum levels of sodium and potassium and blood glucose levels. All study subjects underwent hormonal evaluation for serum levels of cortisol, luteinizing hormone (LH), follicular stimulating hormone (FSH), thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and prolactin (PRL), using principles of electrochemiluminescence immunoassay on Elecsys immunoassay analyzers. Sex of the patient, menstrual phase (if applicable), and time of collection were noted keeping in view the difference in normal ranges. Basal serum cortisol was used to assess adrenal insufficiency and values less than 414 nmol/l was taken as cut off for cortisol deficiency and value between 415 and 690 nmol/l was used as cut off to define relative or functional adrenal insufficiency. This was in accordance with cut offs described by Gonzalez *et al.*, and Marik *et al.*, respectively, considering CNS infection as a stress illness.^[8,9] Patients were diagnosed as central hypothyroidism if

fT4 levels (normal range: 12–22 pmol/l) were low in the presence of low to slightly elevated TSH levels (normal range: 0.27–4.2 mIU/l). Hyperprolactinemia was defined with values more than 15.2 µg/l in men and 23.3 µg/l in women. The normal range for LH was; men: 1.7–8.6 IU/l; women: 2.4–12.6 IU/l in follicular, 14.95.6 IU/l in ovulation, and 1.0–11.4 IU/l in the luteal phase of the menstrual cycle. The corresponding normal range for FSH was; men: 1.5–12.4 IU/l; women: 3.2–12.5 IU/l in follicular, 4.7–21.5 IU/l in ovulation, and 1.7–7.7 IU/l in the luteal phase. Posterior pituitary deficiency was considered in a case having polyuria, polydipsia, and electrolyte disturbances. All patients were treated with specific anti-infectious agents. Statistical analysis was performed using SPSS 12.0 for Windows.

RESULTS

Baseline characteristics of the study patient are shown in Table 1.

A total of 30 patients of acute nonmycobacterial meningitis were taken into study. The cases comprised patients with acute pyogenic meningitis ($n = 23$), viral meningoencephalitis ($n = 4$), brain abscess ($n = 2$), and cryptococcal meningitis ($n = 1$). The mean age of patients was 28.97 ± 11.306 years. Out of 30 patients, 14 (46.7%) were males and 16 (58.1%) were females. The mean hemoglobin in patients was 11.323 ± 1.624 g/dL. The mean total leucocyte count (TLC) of patients was $10,090 \pm 6828 \times 10^9/L$. Hypotension (defined as arm systolic blood pressure (SBP) supine position less than 90 mm Hg) was seen in seven (23.3%) patients. Hypoglycemia (defined as random blood sugar (RBS) by the glucose oxidase method less than 55 mg/dl) was seen in five (16.7%) patients. Hyponatremia (defined as serum sodium by ion selective electrode methods less than 135 mmol/l) was seen in four (13.3%) patients. Hyperkalemia (defined as serum potassium >5 mmol/l) was seen only in one of the patients.

A hormonal profile of study patient is shown in Table 2.

Table 1: Baseline characteristics of patients with acute central nervous system infections

	Mean \pm SD
Age in years	28.9 \pm 13.5
Sex (M:F)	14:16
Hemoglobin (g/dL)	11.3 \pm 1.6
Mean TLC in 10 ⁹ /l	10090 \pm 682
Hypotension	7 (23.3%)
Hypoglycemia	5 (16.7%)
Hyponatremia	4 (13.3%)
Hyperkalemia	1 (3.3%)

Figures in parentheses are in percentage

Table 2: Pituitary hormone profile in patients with acute central nervous system infections

	Patients (n = 30)
Cortisol	
Mean in nmol/L(SD)	1028 (342)
Normal	23 (76.7)
Adrenal deficiency	1 (3.3)
Relative adrenal insufficiency	6 (20)
Prolactin	
Mean in µg/l (SD)	16.08 (13.24)
Normal	21 (70.0)
Hyperprolactinemia	9 (30.0)
LH	
Mean in U/L (SD)	8.24 (9.57)
Normal	24 (80.0)
Low	4 (13.3)
FSH	
Mean in IU/L (SD)	9.86 (13.41)
Normal	27 (90.0)
Low	3 (10.0)
TSH	
Mean mIU/L (SD)	4.02 (0.89)
Normal	27 (90.0)
Low	0 (0)
High	3 (10.0)
fT3	
Mean pmol/L(SD)	4.71 (0.95)
Normal	30 (100.0)
Low	0 (0)
fT4	
Mean in pmol/L(SD)	16.61 (3.92)
Normal	26 (86.7)
Low	1 (3.3)
Presence of multiple pituitary hormone deficiency	3 (10)

Figures in parentheses are in percentage

The mean cortisol level in cases at presentation was 1028.13 ± 1278 nmol/l. One patient (3.3%) had cortisol deficiency. Six patients (20%) were found to have relative adrenal insufficiency. The mean PRL levels in patients were 16.08 ± 13.24 µg/L. Hyperprolactinemia was seen in nine (30%) of the patients. The mean LH levels in patients at presentation were 8.24 ± 9.57 IU/L. The mean FSH levels in cases at presentation were 9.86 ± 13.41 IU/L. Of the 30 patients, LH and FSH were low 4 (13.3%) and 3 (10%), respectively. The mean TSH levels in patients at presentation were 4.02 ± 0.89 mIU/L, while the mean fT3 levels at presentation were 4.71 ± 0.91 pmol/L. The mean fT4 levels in cases at presentation were 16.61 ± 3.92 pmol/L. TSH levels were slightly high in three (0%) and low in none of patients. Free T3 levels were normal in all and fT4 levels were low in one (3.3%) case only. One of the patients had central hypothyroidism defined as low fT4 with normal TSH levels. None of the patients had clinical symptoms and electrolyte disturbances suggestive of central diabetes insipidus.

DISCUSSION

We studied functional abnormalities of the hypothalamic

pituitary axis in 30 patients diagnosed with acute nonmycobacterial CNS infections at the time of presentation. The key findings of the study are that significant numbers of these patients had pituitary hormonal dysfunction at the time of diagnosis; hyperprolactinemia (30%) being the most common, followed by cortisol deficiency (23%). Only one patient had the hormonal profile suggestive of central hypothyroidism.

Infectious diseases of the CNS may cause hypothalamic and/or pituitary dysfunction. Reports of anterior pituitary dysfunction following infectious diseases of the CNS are rare, and the incidence has not yet been studied systematically. Most of these studies have been reported following viral meningoencephalitis. The earliest such case reports came from Hagg *et al*, who reported two cases of persistent hypothalamic pituitary insufficiency (HPI) following acute viral meningoencephalitis due to Coxsackie B5 virus.^[3] Subsequently Kupari *et al*, reported HPI following Influenza A and Herpes Simplex meningoencephalitis.^[4] In a larger case series, HPI was studied in 19 patients following 10–56 after acute CNS infection.^[5] Of all these patients, four suffered from neuroborreliosis, two from encephalitis (two tick-borne encephalitis), and 13 from meningitis (one herpes simplex, one varicella, one enterovirus, 10 of unknown origin). HPI, especially, corticotrophin deficiency was seen in 21% cases and borderline hypogonadotropic hypogonadism was seen in two (11%) cases. None of the patients had somatotrophic or thyrotrophic deficiency or central diabetes insipidus. Isolated posterior pituitary insufficiency has also been described especially in children. In this retrospective analysis, severe CNS infection was associated with central diabetes insipidus in 8 out of 73. The infectious agents were group B streptococcus, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and unknown virus.^[10] Central DI has also been reported in adults with acute CNS infections but in association with multiple pituitary hormone deficiency.^[11,12] Involvement of the hypothalamus with a viral destruction of vasopressin producing neurons seems to be the cause of central DI. In almost all reported cases, the anterior pituitary insufficiency was caused by viruses and only one bacterial meningoencephalitis associated with diabetes insipidus and suspected corticotrophic insufficiency has been reported. A CT of the head revealed a contrast-enhanced suprasellar lesion in this particular patient.^[12] In another retrospective study, GH deficiency was found in 4 of 14 cases after 6–48 months of occurrence of acute meningitis.^[13] Our study is different from the published literature on many accounts. Our study included 30 cases of acute CNS infections which is highest number of cases in the literature so far. We studied HPI at the time of presentation and the majority of our study patients had bacterial meningitis and none of these had posterior pituitary dysfunction.

In this study, we found adrenal deficiency in one and relative adrenal deficiency in six of the 30 patients. The one with adrenal deficiency had unknown viral meningoencephalitis whereas the ones with relative deficiency had encephalitis only. It is reasonable to assume that the incidence and pattern of hormonal deficiencies after acute infectious meningoencephalitis may vary with the type of causative agent, the localization of brain lesion, as well as with the severity of disease. The hormonal deficiencies may be transient, recurrent, or permanent.^[12,13] It has been suggested that focal neurological lesions in the basal regions of the brain might be responsible for an increased risk of hypothalamic–pituitary damage. This is true for patients with tubercular meningitis.^[2,14] None of the patients with adrenal deficiency had any focal neurologic deficiency. In earlier case reports, endocrine investigations and elevated basal PRL levels (probably due to the loss of tonic inhibition of the pituitary lactotrophs by the hypothalamus) were suggestive of a hypothalamic rather than a pituitary lesion.^[5] On the contrary, in other patients, the pituitary gland seemed directly affected.^[15] In our investigation, hyperprolactinemia was seen in nine (30.0%) patients which may reflect stress-induced hyperprolactinemia.

There are few prospective studies of HPI in acute meningitis at the time of presentation. Tsiakalos *et al.*, have recently studied pituitary insufficiency in patients with acute meningitis.^[6] The authors concluded that isolated or combined pituitary deficiencies, which could present at the acute phase and/or occur at a later stage, can develop in a considerable proportion of patients after acute infectious meningitis. During the acute phase, five patients (31.25%) showed apparent pituitary hormone deficiencies: two patients with gonadotropic and three patients with somatotrophic deficiency. The exact status of corticosteroid sufficiency could not be defined in four patients, because no dynamic test was performed in the acute phase. In addition, seven patients (44%) had probable low T₃ syndrome. At 12 months, five patients (31.25%), two with viral and three with bacterial meningitis, had at least one anterior pituitary hormone deficiency. Two patients had isolated corticotrophic and one isolated somatotrophic deficiency. Combined corticotrophic and somatotrophic deficiencies were detected in two patients. New-onset deficiencies accounted for four of those five patients, whereas one patient demonstrated persisting somatotrophic deficiency. All cases of low T₃ syndrome resolved at 12 months. Our results are in line with this pilot study except that we have not studied the somatotrophic status in our study. It has been suggested that the pituitary hormone profile should be done in subjects with CNS infections during the acute phase and as a follow-up to know the extent of

hypothalamic pituitary dysfunction.^[13] One patient had low free T₄ with normal free T₃ and TSH levels suggestive of central hypothyroidism. Also a high level of TSH found in three patients was not associated with any abnormality of free T₃ or T₄. Hence these abnormalities suggest the possibility of disturbances of the hypothalamic pituitary thyroid axis in cases of acute CNS infections.

It is worthwhile to compare HPI in tubercular meningitis and acute nonmycobacterial meningitis (TBM). There is a scarcity of data on HPI in acute meningitis at the time of diagnosis and only one published study is available in the literature.^[2] In this study, 75 patients with TBM were subjected to the pituitary hormonal profile and MRI. The results showed that 32 (42.7%) cases showed relative or absolute cortisol insufficiency. Twenty-three (30.7%) cases showed central hypothyroidism and 37 (49.3%) cases had hyperprolactinemia. No patient had evidence of diabetes insipidus. Multiple hormone deficiency was seen in 22 (29.3%) cases. MRI of the hypothalamic pituitary axis using dynamic scanning and thin cuts revealed abnormalities in 10 (13.3%) of the cases. The comparison with this study suggests that hypothalamic pituitary abnormalities are more common in TBM as compared to nonmycobacterial acute CNS infections. The possible mechanisms of HPI in TBM are direct involvement of pituitary gland, vasculitis, or/and basal meningitis.

The major limitation of our study is that we did not carry out dynamic tests for pituitary hormone deficiency especially adrenocorticotrophic hormone (ACTH) stimulation for secondary adrenal deficiency. Diagnostic value of ACTH stimulation test for secondary adrenal insufficiency is compromised during the first 4 weeks after pituitary insult because during this period adrenal glands will still respond to exogenous ACTH stimulation despite the loss of endogenous ACTH drive.^[16] Further, standard corticotrophin stimulation test lacks sensitivity, and the insulin tolerance test is associated with adverse events such as seizures therefore unsafe in tubercular meningitis.^[17,18] Alternatively, adrenal insufficiency can also be diagnosed using basal serum cortisol in acute critically ill patients and we opted for this method.^[8,9] We did not carry out imaging of the hypothalamic pituitary axis and also did not study reversibility of pituitary dysfunction after treatment. Further detailed studies are needed to study HPA including sex hormones and growth hormone in this subset of patients.

In conclusion, hypothalamic pituitary hormonal dysfunction is not uncommon in newly diagnosed patients with acute nonmycobacterial meningitis. The most common hormonal abnormalities seen were adrenal insufficiency and hyperprolactinemia. Further studies are needed to

evaluate PHA using dynamic pituitary tests and MRI in subjects with acute CNS infections.

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