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Anterior pituitary function in patients of meningoencephalitis: An observational longitudinal study from eastern India

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Abstract
Aim and Objective: To study the anterior pituitary functions in patients of meningoencephalitis and also the prevalence of anterior pituitary dysfunction at diagnosis and at six months follow up of patients of meningoencephalitis.
Materials and Methods: Observational, longitudinal**,** hospital-based, single centre study included 100 patients admitted in the medicine & neuro-medicine department of IPGME&R, Kolkata who diagnosed with meningoencephalitis. Blood investigations like Complete blood count., Blood urea and creatinine, Fasting and post prandial serum glucose, Lipid profile, Serum Sodium and potassium, Anterior pituitary hormone test-Thyroid stimulating hormone(TSH), FT4, FSH, LH, IGF1, Prolactin, Cortisol, ACTH, HbA1c and other relevant investigations was done.
Results: Anterior pituitary dysfunction is common with meningoencephalitis, most common being low IGF1 (47%) followed by low FSH (35%). Not much significant difference has been found among TBM and non TBM cases. Multiple hormone deficiency among 45.2% TBM Cases while 53.1% non TBM cases. Many patients with hormonal deficit at baseline found to recover at 6 month while new cases (two cases of central hypothyroidism & low IGF1, 7 cases of low FSH & LH, five cases of hypocortisolism) develop deficiency at 6 month.
Conclusion: A high index of clinical suspicion is required to identify HPI following CNS infections condition in both acute settings and in the long-term follow-up of patients.

Keywords: tubercular meningitis (TBM), bacterial meningitis (BM), hypothalamo-pituitary insufficiency (HPI), anterior pituitary hormones, IGF 1(Insulin like growth factor 1) and FT 4 (Free T4)

Introduction

Meningitis is the most common infection associated with mortality and morbidity worldwide, thus posing serious public health burden demanding early diagnosis and treatment. Despite advancements in antimicrobial therapy, the prevalence of mortality remains high, especially in developing countries, among adults. Annual incidence of meningoencephalitis in U.S. is >2.5 cases per 1 lac population [1] while in India it is approx. 2.3 cases per lakh population in some community based studies while in others it is >3/lac. Bacterial meningitis is usually a part of bacteremic illness, although direct spread from adjacent foci in ear, skull fracture or sinus can be causative. Hearing loss is a frequent complication. An obliterative endarteritis of the leptomeningeal arteries passing through meningeal exudate may produce secondary cerebral infarction. Pituitary hormones are involved in for responding appropriately to stress and maintaining vital body functions as well as many other functions. Basal hormone measurements are used in evaluating pituitary functions in addition to clinical findings [2, 3]. Infectious causes are increasingly being identified as an important cause of hypopituitarism. The clinical findings of pituitary deficiency [4] depend on missing hormone, the degree of hormone deficiency and onset. Hormone deficiency in hypopituitarism due to pituitary compression or destruction occurs in the following order: GH, FSH, LH, TSH and ACTH deficiency. PRL secretion is affected latest. Main presentation during childhood was growth retardation while hypogonadism is the earliest symptom in adults. Here we have planned to observe the anterior pituitary function in of meningoencephalitis group of patients and correlate this with overall morbidity and mortality after a follow up period of six months to document outcomes to modulation of their therapy.

Materials and method

Observational, longitudinal**,** hospital-based, single center study conducted by medicine & neuromedicine department of IPGME&R, Kolkata on diagnosed with meningoencephalitis. The total number of patients under study was 100 with study period From February 2016 to July 2017.
During the first study visit, written informed consent was obtained from the patients or their relatives, as required.
A detailed history like smoking, hypertension, diabetes, weakness, cold intolerance. H/O fever, alteration of sensorium, seizure, bowel/bladder incontinence, contact or past H/O tuberculosis, any pressure ulcers. Family history was documented if any.
General investigation like blood pressure, pulse, skin lesions if

any, lymph nodes, weight, JVP, pallor, oedema, and thyroid gland examination was done at the time of admission.
Routine investigations like Complete blood count, Blood urea and creatinine, Fasting and post prandial serum glucose, Lipid profile, Serum Sodium and potassium was done by collecting the blood samples at the time of admission. Special tests were performed to identify anterior pituitary functions in patients like IGF1, FSH, LH, TSH, FT4, ACTH, Cortisol, Prolactin and HbA1c at the time of admission and follow up at 6 months.

Statistical analysis
For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. P-value ≤ 0.05 was considered for statistically significant.

Results
A total of 37% of participants were male, while 63% were female in which Tubercular meningitis (TBM), bacterial meningitis (BM) and meningoencephalitis (ME) were found in 53%, 32% and 16% accordingly.
IGF1, FSH, LH, TSH, FT4, ACTH, Cortisol and Prolactin levels were checked at the time of admission and follow up at 6 months were shown in Table 1.The significant changes were found in FSH (0.0064), LH 1(0.0163), ACTH (<0.0001), FT4 (0.0458) and Prolactin (0.0001) respectively**.**
The significant changes in BM patients have been seen in FSH (0.202), ACTH (0.0011), and Prolactin (0.0037) respectively. In ME patients, ACTH (0.0065) level was found abnormal significantly. ACTH (0.00029) and Prolactin (0.0237) levels were changed significant in TBM patients. %). No significant difference has been found among TBM and non TBM cases. Multiple hormone deficiency among 45.2% TBM Cases while 53.1% non TBM cases.

Table 1: Hormonal Profiling of study subjects

Parameters	Above Normal	Below Normal	Abnormal	Normal	P Value
FSH					
Admission	-	35	-	18	0.0064
After 6 Months	-	65	-	82	
LH_1					
Admission	15	-	-	85	0.0163
After 6 Months	19	7	-	74	
Cortisol					
Admission	1	19	-	80	0.4444
After 6 Months	0	15	-	85	
ACTH					
Admission	-	-	99	1	<0.0001
After 6 Months	-	-	71	29	
IGF 1					
Admission	4	47	-	49	0.6799
After 6 Months	3	53	-	44	
TSH					
Admission	2	7	-	91	0.1744
After 6 Months	4	2	-	94	
FT4					
Admission	5	7	-	88	0.0458
After 6 Months	0	4	-	96	
Prolactin					
Admission	32	-	-	68	0.0001
After 6 Months	8	1	-	91	

(p-value ≤ 0.05 was considered for statistically significant)

Thyroid-stimulating hormone (TSH), growth hormone (GH), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and adrenocorticotropic hormone (ACTH), IGF 1(Insulin like growth factor 1) and FT 4 (Free T4).

Discussion
We have conducted an observational longitudinal study of meningoencephalitis cases over a period of februray 2016 to July 2017.Total 100 patients of meningoencephalitis were included in the study.
CSF study was the cornerstone in segregating the cases into 3 groups of pyogenic meningitis (31 cases), tubercular meningitis (53 cases) and viral meningitis (16 cases).
The key findings of the study are that significant numbers of these patients had pituitary hormonal dysfunction at the time of diagnosis; low IGF1 (47%) being most common, followed by low FSH (35%) being the 2nd most common, followed by hyperprolactinemia (32%) & cortisol deficiency (19%). Almost all patients had high ACTH (99%) value probably stress related.7 patients had low TSH and FT4 value.

Dhanwal *et al*., who studied 30 untreated adult patients with acute meningitis, meningoencephalitis or encephalitis, due to various non-mycobacterial agents (acute pyogenic meningitis (n = 23), viral meningoencephalitis (n = 4), brain abscess (n = 2), and cryptococcal meningitis). Adrenal insufficiency both absolute and relative was seen in seven (23.3%) and hyperprolactinemia was seen in nine (30.0%). One had central hypothyroidism and seven (23.3) showed low levels of LH and/or FSH. Our findings also correlated with a recent study conducted on 16 patients with acute infectious meningitis to investigate whether autoimmune mechanisms could play a role in the pathogenesis of acute meningitis-induced hypopituitarism and the patients were evaluated in the acute phase, and at 6 and 12 months after the acute meningitis. In the acute phase, 18.7% of the patients had GH deficiency and 12.5% had ACTH and FSH/LH deficiencies. At 12 months after acute meningitis, 6/14 (42.8%) had GH deficiency, 1/14 (7.1%) had ACTH, FSH, and LH deficiencies, 2/14 (14.3%) had combined hormone deficiencies, and 4/14 (28.6%) had isolated hormone deficiencies at 12 months. Four of nine (44.4%) of hormone deficiencies at 6 months were recovered at 12 months, and three of eight (37.5%) hormone deficiencies at 12 months were new-onset hormone deficiencies.

Tanriverdi *et al*. [5] showed the occurrence of anti-pituitary antibodies (APA) and anti-hypothalamus antibodies (AHA) for the first time, during the acute phase of meningitis, as well as 6 and 12 months later. The frequency of antibody positivity ranged from 35 to 50% of the patients throughout the 12-month period. The presence of a substantially high frequency of AHA and APA after acute meningitis suggests that an autoimmune hypothalamic-pituitary process could be triggered by acute meningitis. However, an analysis of the relationship between pituitary dysfunction and the presence of the antibodies at any time during the follow-up period showed no significant correlation. The lack of correlation was assumed to be due to the short duration of the prospective follow-up.

Limitations

Our study may have several limitations. First, our institution is a referral centre and hence the population studied may not be representative of the general population and probably we are dealing with more complicated cases with more frequent anterior pituitary involvement. The study design may not be adequate to establish a cause and effect relation between the studied variables and underlying disease. Sample size need to be more robust to come to a definite conclusion. Furthermore, prospective studies are required to clarify the possible mechanisms underlying pituitary dysfunction during and following such infectious diseases.

Conclusion

HPI following CNS infections is an important clinical entity, especially in the tropics, and a high index of clinical suspicion is required to identify this condition both in the acute settings and in the long-term follow-up of patients. Further studies should focus on the impact of HPI and its early recognition and treatment in the mortality and morbidity of CNS infections and to clarify the possible mechanisms underlying pituitary dysfunction during and following such infectious diseases.

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