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Gene Xpert As A Prognostic Marker In Adult Immunocompetent Tubercular Meningitis Patients

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I. INTRODUCTION :

Tuberculosis (TB) is caused by bacteria of the Mycobacterium Tuberculosis complex.TB is classified as pulmonary or extra - pulmonary (lymph node , pleural TB , upper airways , genitourinary , skeletal TB , tubercular meningitis and tuberculoma , gastrointestinal ,pericardial , miliary or disseminated tuberculosis). It is estimated that about one-third of current global population is infected asymptomatically with tuberculosis , of whom 5-10 % will develop clinical disease during their lifetime.Globally 6.7 million cases of tuberculosis were reported in 2017 out of which 2.84 million cases were reported from india.**(1)**

TB of the central nervous system accounts for 5% of extrapulmonary cases .Though more common in immunocompromised adults (like HIV positive patients) it also occurs in immunocompetent adults. Tubercular meningitis results from hematogenous spread of primary or post-primary pulmonary or from the rupture of subependymal tubercle into the subarachnoid space. disease often presents as subtly as headache and slight mental changes after a prodrome of weeks of low grade fever , malaise , anorexia and irritability .it may also evolve acutely with severe headache , confusion , lethargy , altered sensorium and neck rigidity .**(2)**

Lumbar puncture is the cornerstone of diagnosis.In general , examination of cerebrospinal fluid(CSF) reveals high leucocyte count with lymphocytic predominance (upto 1000/ul), a protein content of 1-8 g/L , a low glucose concentration and increased adenine deaminase (usually more than 10 IU/L but varies with different labs).however any of the parameters can be normal. AFB are infrequently seen in CSF sediment. culture of CSF is diagnostic in upto 80% cases and remains the gold standard. real time automated nucleic acid amplification(xpert MTB /RIF assay) has a sensitivity of upto 80% and is preferred initial diagnostic option . treatment should be initiated immediately upon a positive XPERT MTB/ RIF result . A negative test does not rule out exclude a diagnosis of Tubercular meningitis and requires further diagnostic work up. Imaging studies (CT AND MRI) may show hydrocephalus and abnormal enhancement of basal cistern or ependyma .**(2)**

The current retrospective cohort study aims to study the prognostic significance of XPERT MTB/RIF in tubercular meningitis by comparing the incidence of various complication (stroke , hydrocephalus , cranial palsy and epileptic seizures) between control group (diagnosed cases of tubercular meningitis but CSF negative for xpert MTB /RIF) AND study group (diagnosed cases of tubercular meningitis and CSF positive for xpert MTB /RIF).

keywords: tubercular meningitis , prognostic factors , immunocompetent adults

II. METHODS AND MATERIALS:

A descriptive retrospective cohort study was conducted at patna medical college and hospital between august 2018 and december 2019 . follow up cases of tubercular meningitis coming to OPD or as inpatients were selected on strict inclusion and exclusion criteria .

Inclusion criteria a) diagnosed cases of tubercular meningitis (based on typical clinical history AND cerebrospinal fluid findings - increased protein , lymphocyte predominant moderate leucocytosis and ADA more than 10 IU/L AND typical imaging finding in CT/MRI brain) b) absence of any primary or secondary immuno-deficiency(HIV , post organ-transplant , therapeutic use of immunosuppressants including corticosteroids) c) positive xpert MTB /RIF in CSF for study group and negative xpert MTB /RIF in CSF for control group .

exclusion criteria : a) all cases of tubercular meningitis where clinical or cerebrospinal findings or radiological findings were not typical of tubercular meningitis b) presence of primary or secondary immunosuppressed state c) patients on long term immunosuppressants .

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the study and control group was divided as follows:

study group (25 cases) : diagnosed cases of tubercular meningitis (based on clinical AND radiological findings AND typical CSF findings of lymphocyte predominant leucocytosis moderately raised protein and ADA more than 10 IU/L.) **AND positive xpert MTB /RIF in CSF.**

control group(25 cases) : diagnosed cases of tubercular meningitis (based on clinical AND radiological findings AND typical CSF findings of lymphocyte predominant leucocytosis moderately raised protein and ADA more than 10IU/L.) **AND negative xpert MTB /RIF in CSF.**

The incidence of various complications - stroke , cranial nerve palsy , hydrocephalus and epilepsy was determined based on clinical history and review of medical records.The findings of both groups were compared and results were compared and analysed using standard statistical methods to derive conclusions.

III. RESULTS AND STATISTICAL ANALYSIS :

STATISTICAL ANALYSIS

Descriptive statistics including frequency, mean and standard deviations were calculated for the demographic data and clinical features. Categorical variables were presented as percentage; continuous variables were presented as mean along with 95% confidence limit. The associations of disease complications with the outcome were analysed by univariate analysis. For all tests, a one-sided P value ≤0.05 was considered statistically significant. All statistical analyses were performed using Epi info version 7.2.

IV. RESULTS

In this study a total of 50 patients were recruited in which 31(62%) were males and 19 (38%) were females. Gender distribution of the patients are as follows:

GeneXpert result	Male	Female	Total
Positive	15(60%)	10 (40%)	25 (100%)
Negative	16 (64%)	9 (36%)	25 (100%)

Age distribution of the patients

Mean age of the patients in Genexpert positive and negative groups were 46.8 (95%CL; and 45.8 years with no statistical difference (p value = 0.8)

Age group	Genexpert positive	Genexpert Negative
0-20	0	0
20-40	11	11
40-60	7	8
60-80	7	6
80-100	0	0
TOTAL	25	25

Clinical features

CLINIAL FEATURES	GENEXPERT POSITIVE	GENEXPERT NEGATIVE	Fisher Exact P value (one – tailed)
Stroke	13(52%)	6 (24%)	0.03

Hydrocephalus	12 (48%)	4 (16%)	0.04
CN palsy	15 (60%)	10 (40%)	0.016
Epileptic seizures	16 (64%)	9 (36%)	0.12

All clinical features are more commonly found in Gene-xpert positive patients. Stroke, hydrocephalus and CN palsy were significantly more common in Gene-xpert positive patients ($p < 0.05$)
Rifampcin resistance was not found in any of the patients.There was no mortality in the study or control group.

V. REVIEW OF LITERATURE AND DISCUSSION :

Various studies have been conducted to study the prognostic factors in tubercular meningitis. The study conducted by C H Lu et al in 2001 found that significant prognostic factors in Tubercular meningitis include severity of TBM at admission , presence of headache, fever , hydrocephalus , high protein CSF concentration and high CSF lactate level.(3) . the study conducted by Jin Gu , Heping Xiao and Wenwen Sun found that advanced age , changes in consciousness , low GCS score and concomitant hydrocephalus were adverse prognostic factors for TBM.(4) . study conducted by Lan Wen , Maolin Li , and Kunyi Li concluded that advanced stage of disease , hydrocephalus , altered consciousness , advanced age and cerebral infarction were risk factors for death in tubercular meningitis (5)

No studies so far have been conducted to determine the prognostic value of genexpert in CSF for tubercular meningitis . The current study has indicated that genexpert positivity in CSF is also a prognostic indicator for tubercular meningitis as complications like stroke , cranial nerve palsy and hydrocephalus are significantly more common in study group tubercular meningitis patients as compared to control group. However larger studies are required for validation of this conclusion.

VI. CONCLUSION :

A) GENE-XPERT in CSF should be mandatorily done in all cases of tubercular meningitis as part of initial evaluation as this has high sensitivity(upto 80%)(1) for diagnosis of tubercular meningitis . it facilitates quick diagnosis ,early initiation of anti tubercular therapy and also is predictor of adverse outcomes like stroke , cranial nerve palsy and hydrocephalus.
B) Though culture of csf is gold standard for detection of drug resistant cases of tuberculosis but gene- xpert testing of CSF facilitates quick identification of rifampicin resistance .
C) The current study has indicated the prognostic value of gene xpert in CSF in cases of tubercular meningitis as complications like stroke , cranial nerve palsy and hydrocephalus are significantly more common in study population. Therefore all patients of tubercular meningitis with positive genexpert in csf can be considered high risk cases and aggressive treatment strategy (early initiation of therapy , corticosteroids and antiepileptic drugs etc) can be taken for these high risk cases. However this requires validation by larger studies.
D) In addition to this various studies have identified that hydrocephalus , high protein and lactate in csf , advanced age , poor GCS , cerebral infarction are other classical poor prognostic factors in tubercular meningitis.

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