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MANAGEMENT OF ANTI-TUBERCULAR THERAPY INDUCED HEPATITIS AND TUBERCULOUS MENINGITIS COMPLICATIONS IN A YOUNG ADULT PATIENT: A CASE REPORT

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Abstract:
Tuberculous Meningitis (TBM) is the most dreaded form of tuberculosis (TB) with Central Nervous system involvement which has very high morbidity and mortality rate. It is noted in 5 to 10% of extra pulmonary TB cases, and accounts for approximately 1% of all Tuberculosis cases. Multi-drug regimen includes Isoniazid, Rifampin, Ethambutol, Pyrazinamide and Streptomycin along with adjunctive treatment with corticosteroids is required in the effective management of Tuberculosis meningitis. Anti-Tuberculosis Therapy induced Hepatotoxicity is the well-known side effect of several drugs which are used for the treatment of TB and it is found to be 2% to 28%. We report a case of ATT induced hepatitis (Isoniazid-Rifampin) along with tuberculosis meningitis complications such as grade II Obstructive Hydrocephalus and hyponatremia and it is successful management with Inj.Mannitol and Inj.Dexamethasone.

Key Words: *Tuberculous Meningitis, ATT induced Hepatitis, Hydrocephalus, Hyponatremia*.

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INTRODUCTION:

Tuberculous Meningitis (TBM) is a chronic infection of meninges caused by *Mycobacterium Tuberculosis*, mainly affected through tissues lining the brain and spinal cord [1], which is very often seen in children and adults in India. Although there has been a reduction in the number of patients with TBM, it is estimated that in India the mortality is approximately 1.5/100,000 population [2]. TBM is a sub-acute disease in which symptoms were present for a median of 10 days prior to diagnosis. Clinical presentation includes low grade fever, malaise, head ache, dizziness, vomiting and/or personality may persist for few weeks (prodromal phase), after which patients can develop more severe head ache, altered mental status, stroke, hydrocephalus and cranial neuropathies [3]. Risk factors usually include age (children> adults), HIV Co-infection, malnutrition, measles in children, alcoholism, malignancies, use of immunosuppressive agents in adults [4]. Diagnosis of TBM is based on five features which are independently associated with age, length of history, white blood cell count, total cerebrospinal fluid (CSF) white cell count and CSF neutrophil proportion [5]. In TBM, potential complications include associated increased intracranial pressure (ICP), hydroencephalus, vasculitis, acute seizures and hyponatremia [6].

Management of TBM requires multi-drug treatment and drugs should adequately cross the blood brain barrier to achieve therapeutic concentration in CSF. First line agents for treatment of TB include Isoniazid, Rifampin, Pyrazinamide and Ethambutol. Second line agents (Streptomycin) are less effective and have more adverse effects than Isoniazid and Rifampin based regimens. ATT (Anti Tuberculosis Therapy) induced hepatotoxicity is the most common adverse effect leading to interruption of therapy. Apart from these skin rashes, gastro intestinal and neurological disorders also noticed [7,8]. Death from TBM strongly associated with delayed diagnosis and appropriate treatment [6].

CASE REPORT:

A 30 year old male patient was admitted with the complaints of nausea, hiccups, anorexia, vomiting for 3 days, previously diagnosed with FUC of disseminated Koch's with TBM on ATT like cap. Isoniazid-Rifampin 450mg, Tab. Pyrazinamide 750mg, Tab. Ethambutol 800mg and Inj. Streptomycin 1gm. Before the initiation of ATT regimen, liver function tests were shown to be normal. He is neither a smoker nor alcoholic.

On physical examination, he is alert and oriented with the following vital signs: Blood Pressure 110/70 mmHg, Pulse rate 80 bpm, Temperature: 37.2°C and Respiratory Rate: 22 bpm. Clinical parameters illustrated in table no.1, the patient liver function test and hematological parameters were abnormal, based on this reports, the physician diagnosed as Isoniazid-Rifampin induced Hepatitis. Immediately the drug was stopped and continued with Tab. Ethambutol 600mg OD, Inj. Streptomycin 1000mg OD along with Tab. Levofloxacin 750mg OD, Tab. Pyridoxine 40 mg OD, Tab. NVM M12(Multivitamin). The patient's Liver Function Test and anemic biomarkers were closely monitored and shown to be improved gradually.At the time of discharge, physician restarted Cap. Rifampin-Isoniazid 450mg once the Liver Function test becomes Normal. After 10 days again patient was admitted with headache, nausea, and left eye pain for 2 days. Chest X-ray shows Normal. MRI and NCCT scan shows grade II obstructive hydrocephalus and serum sodium level was reduced, which are the complications of TBM. Patient undergone Ventriculoperitoneal shunt placement technique and managed with Inj. Mannitol 100ml IV BD and Inj. Dexamethasone 8mg TDS and after few days dose tapered to 4mg BD.Patient relieved his symptoms gradually and was clinically stable at the time of discharge.

Table 1: A Summary of Clinical Course Of Patient

Parameters	16/1/2015	26/2/2015	5/2/2015	16/2/2015	28/2/2015	Reference value
	At the time of ATT initiation	ATT Induced Hepatitis	At the time of discharge after recovery from ATT induced Hepatitis	Re-admission with Obstructive Hydrocephalus	At the time of discharge after recovery of Obstructive Hydrocephalus	
WBC	11.5×10^3 cells/mm^3	14.5×10^3 cells/mm^3	11.6×10^3 cells/mm^3	16.8×10^3 cells/mm^3	12.3×10^3 cells/mm^3	$4.5\text{-}10\times10^3$ cells/mm^3
Platelet	180×10^3 cells/mm^3	162×10^3 cells/mm^3	148×10^3 cells/mm^3	198×10^3 cells/mm^3	292×10^3 cells/mm^3	$150\text{-}400\times10^3$ cells/mm^3
Hemoglobin	12.6 g/dl	10.9 g/dl	11.5 g/dl	11.8g/dl	12.0g/dl	13.5-17g/dl
Hematocrit	42.2%	34.2%	37.8%	35.5%	37.0%	37-47%
MCH	28..4pg	26.4pg	29.3pg	27.2pg	26.0pg	27-31pg
RDW-	13.6%	15.3%	12.6%	13.5%	13.8%	11.6-14.4%
Alkaline Phosphatase	34IU/L	172 IU/L	148IU/L	132 IU/L	127 IU/L	36–141 IU/L
AST	38IU/L	259 IU/L	62IU/L	43 IU/L	35 IU/L	5–45 IU/L
ALT	26 IU/L	679 IU/L	55IU/L	42 IU/L	42 IU/L	5–45 IU/L
Serum.TotalBilirubin	0.4mg/dl	9.04mg/dl	3.2 mg/dl	1.5mg/dl	0.7 mg/dl	0.3-1mg/dl
Direct Bilirubin	0.1 mg/dl	7.01 mg/dl	1.2 mg/dl	0.8 mg/dl	0.4 mg/dl	0-0.3mg/dl
Indirect Bilirubin	0.2mg/dl	4.2mg/dl	1.8 mg/dl	1.3mg/dl	0.3mg/dl	0.2-0.7mg/dl
Sodium	126 mEq/ml	138 mEq/ml	142mEq/ml	118mEq/ml	132mEq/ml	135-145mEq/ml

DISCUSSION:

The treatment of extra-pulmonary TB follows standard RNTCP treatment guidelines depending upon categorization, consistent with International recommendations by WHO and International Union against Tuberculosis and Lung Disease (IUATLD). The patients with severe extra-pulmonary TB are treated with RNTCP category I regimen consisting of initially, two month Isoniazid, Rifampicin, Pyrazinamide and Ethambutol given thrice a week followed by four month continuation phase of Isoniazid and Rifampicin given thrice a week. [9]. Our case report highlights ATT induced Hepatitis and a rare TBM complications like grade II Obstructive Hydrocephalus, Hyponatremia. During the follow-up, after initiation of ATT regimen the patient liver function tests was found to be abnormal and it is suspected as ATT induced Hepatitis, which is effectively managed by with drawl of causative drugs (Isoniazid and Rifampicin). The patient was closely monitored for elevated liver enzymes, found to be normal after stopping

Isoniazid and Rifampicin and discharged in stable condition with re-initiation of above drugs to overcome the multi drug resistant TB. When the patient came for next visit, he complained recurrent head ache, nausea, vomiting, left eye pain. Examination of Non-contrast CT (NCCT) and MRI of brain revealed grade II Obstructive Hydrocephalus, sodium levels was found to be abnormal (118 mEq/ml) which are one of the complications of TBM. Due to early diagnosis, followed with Ventriculoperitoneal shunt placement technique leading to improved neurological outcomes. Patient was further managed with administration of Inj.Dexamethasone 8 mg IV TDS and Inj. Mannitol 100ml IV BD. In a study conducted by Grace E Marx *et al*., patients diagnosed with Hydrocephalus, who underwent shunt replacement demonstrated favorable outcomes in 33%-45%, suggesting that there may be a role for surgical intervention in advanced TBM hydrocephalus [(3)]. According to WHO guidelines, steroids should be used initially in hospitalized of TBM and gradually reduce dose in over 6-8 weeks [9].

CONCLUSION:

Meningitis is the most deadly form of TB, a high index of clinical suspicion, timely and judicious use of invasive diagnostic methods and confirmation of diagnosis and close clinical monitoring for Adverse Drug Reactions are the key to the successful management of TBM with complications.

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