Original Article

Monitoring of Adverse Drug Reactions in adult Tubercular Meningitis Patients Under Standard Therapeutic Regimen at a North Indian Tertiary Care Centre: An Observational Study

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ABSTRACT

Adverse drug reactions are the leading cause of mortality and morbidity in healthcare and have a major financial impact on healthcare resources. Adverse drug reactions account for 6.7% of hospital admissions and 10 to 20% of hospitalized patients. The impact and management of adverse drug reactions are challenging as they could result in increased costs from frequent hospitalization, extended hospital stays, further investigations, and, in more severe cases, drug therapy. Studies have demonstrated that adverse pharmacological reactions to anti-tubercular medications can have a poor impact on compliance, abrupt discontinuation of therapy, and indirectly lead to multidrug resistance. As a result, it is essential to monitor adverse drug reactions and report them so that the causative drug can be found and the patient can get the proper therapeutic regimen. Pharmacovigilance of anti-tubercular drugs is crucial for the effective treatment of tuberculosis and for its elimination. Maximum number of patients developing ADR reported with GIT symptoms reflecting the fact that ATT drugs irritate GIT of maximum patients. Hepatitis also seen in maximum patients indicating the role of monitoring of LFT during the therapy. On assessment of causality through WHO UMC scale, maximum adverse drug reaction has been categorized under "possible" followed by category of "probable" suggesting that due to lack of rechallenging in the rechallenging, in the process of causality assessment none of the ADR could be grouped under "definite".

Keywords: Tubercular meningitis, Adverse drug reactions, Pharmacovigilance.

INTRODUCTION

CNS tuberculosis accounts for 1% of all tuberculosis cases and 6% of extra pulmonary tuberculosis in immunological competent people. With an increase in TB infection, CNS TB incidence rises. According to estimates, the CNS is affected in 10% of all tuberculosis patients.[1] Considering that 10% of cases are CNS TB, the incidence of CNS TB in India in 2016 was almost 21.2/100,000 people.[2] The estimated mortality rate from tuberculous meningitis in India is 1.5 per 100,000. HIV infection raises the risk of complications and case fatality rates for extra pulmonary tuberculosis, especially tuberculous meningitis.[3] The most severe form of CNS tuberculosis, tuberculous meningitis, significantly increases morbidity and morbidity in both adults and children. The prognosis is often poor and left patient with disabilities especially in immunocompromised[4]. Overall hospital mortality rates for individuals with drug-susceptible TBM can reach 50%, and long-term five-year mortality rates can reach 58%. Due to illness complications such infarction, vasculitis, and hydrocephalus, people with TBM very frequently experience long-term neurological consequences. Delays in diagnosis and subsequent early initiation of anti-TB treatment, as well as limited CSF penetration of many anti-TB agents like rifampin, are contributing factors to the high rates of morbidity and mortality among TBM patients[5]. WHO recommendation for TBM includes two month of four drug regimen (rifampicin, isoniazid, pyrazinamide and ethambutol) in both adult and children, followed by 7 to 10 month of isoniazid and rifampicin. [6]

According to the index TB panel, TBM should be treated for at least 12 to 18 months. It is hypothesized that adjunct corticosteroids reduces the inflammation in TBM and thereby increase patient outcomes[7].

According to a 2016 Cochrane Systematic Review and Meta-analysis, corticosteroids improve survival in TBM (children and adults) who are HIV-1 negative. For the recommended dosage of steroids in TBM, the Index TB guideline state that "In hospital: intravenous dexamethasone 0.4 mg/kg/24 hr in 3–4 divided doses may be preferred with a slow switch to oral therapy and taper". Treatment guideline recommends adjunctive corticosteroids for 6 to 8 weeks. In our setup, as a standard therapeutic regimen, HRZS for 3 months and HRZ for 7 to 10 months with dexamethasone 8 mg TDS is used.

According to World Health Organization (WHO), adverse drug reaction is defined as "Any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function". Anti-tubercular drugs affect essentially all of the body's systems, especially the gastrointestinal, liver, skin, neurological system, and eyes, as with many other drugs.[8] It's the main cause of the treatment non-adherence and therapeutic failure; these adverse drug reactions pose a challenge to the successful treatment of the patients[8,9].

Adverse drug reactions are the leading cause of mortality and morbidity in healthcare and have a major financial impact on healthcare resources. Adverse drug reactions account for 6.7% of hospital admissions and 10 to 20% of

hospitalized patients. The impact and management of adverse drug reactions are challenging as they could result in increased costs from frequent hospitalization, extended hospital stays, further investigations, and, in more severe cases, drug therapy[8,10]. Studies have demonstrated that adverse pharmacological reactions to anti-tubercular medications can have a poor impact on compliance, abrupt discontinuation of therapy, and indirectly lead to multidrug resistance. As a result, it is essential to monitor adverse drug reactions and report them so that the causative drug can be found and the patient can get the proper therapeutic regimen. Pharmacovigilance of anti tubercular drugs is crucial for the effective treatment of tuberculosis and for its elimination[8,11]. Pharmacovigilance of ATT drug ensures detection, understanding, assessment and prevention of adverse events. The frequency, intensity, and nature of adverse drug reactions (ADRs) caused on by anti-TB treatment have always been of concern. The overall incidence of adverse drug reactions (ADRs) caused by anti-TB drugs ranges from 5.1% to 83.5%[12]. ADR's frequency and expression may be influenced by variables such demographic, genetic, dietary, and co-morbidities[11].

Continuous monitoring of ADRs, especially in public health programmes that treat for a large number of patients, particularly in the case of diseases like tuberculosis where early detection and effective management of ADRs might affect adherence and, thus, the success of therapy[13].

Most anti-tubercular medications fall into the first- and second-line pharmacological groups. The five first-line medications are H (isoniazid), R (rifampicin), Z (pyrazinamide), E (ethambutol), and S (sertraline) (Streptomycin). The thioamides ethionamide and prothionamide, the aminoglycosides kanamycin and amikacin, capreomycin, PAS, cycloserine, terizidone, and several fluoroquinolones like moxifloxacin, levofloxacin, and gatifloxacin are among the second-line medications. These first-line medications are all linked to a number of adverse effects[14]

METHODOLOGY

The study as was conducted at the Department of Neurology and Department of Respiratory Medicine, King George's Medical University, Lucknow. It started after the ethical clearance from the University's Institutional Ethics Committee (vide no: VII-PGTSC-IIA/P2). All patients with diagnosed case of tuberculous meningitis with proper written consent were srecruited from the Departments of Neurology and Respiratory Medicine, KGMU. The study duration was 12 month i.e October 2021 to September 2022.

Subject selection:

All the patients with diagnosed or proven tuberculous meningitis were screened for the study. Those who satisfied our inclusion/exclusion criteria were included in the study after the written consent is taken.

Setting:

Study will be conducted in the Department of Pharmacology in collaboration with Department of Neurology and Respiratory Medicine and cases taken from IPD or OPD

Inclusion criteria

- Age >18yrs
- Both gender(male and female)
- With written consent
- Diagnosed case of TBM based on laboratory, neuroimaging and clinical features
- TBM cases with hydrocephalus
- TBM cases with tuberculoma
- Cases of pulmonary TB with TBM as a complication

Exclusion criteria

- Age <18yrs
- Patients who were unwilling to participate and did not give consent in the study.
- Pregnant and Lactating women
- Patients with viral and bacterial meningitis (except tuberculous meningitis), cerebral abscess, meningeal metastasis and Lymphoma.
- TBM infected with HIV
- Drug resistant TBM i.e MDR and XDR cases.
- Patients with chronic liver disease and renal diseases as these affects ADR monitoring
- Patients with incomplete medical record
- Patients lost to follow up.

Study design

It is a Prospective observational study. Diagnosis of TBM is made on the basis of presence of *mycobacterium tuberculosis* in CSF, clinical and radiological imaging. Patients who satisfy above criteria are categorized into three groups A, B and C.

Group A consist of TBM patients without tuberculoma without hydrocephalus

Group B consist of TBM patients with tuberculoma,

Group C consist of TBM patients with hydrocephalus.

On admission demographic details are taken. After the initiation of standard therapeutic regimen, now patients are monitored for 12 months for development of ADR using WHO UMC causality assessment scale and severity assessed using Hartwig Siegel severity scale. During stay in the hospital or after discharge or on follow up patients and their care givers and nursing staffs (for admitted patients)

are instructed to report any form of adverse drug reactions directly or telephonically which is recorded in suspected adverse drug reaction reporting form issued by Indian pharmacopeia commission under Pharmacovigilance programme of India, Govt of India.

Sample Size

Sample Size at 90% Power

Sample size is calculated on the basis of maximum variation in modified Rankin

Score among various groups of TBM based on diagnosis using the formula,

$$n = k\frac{\left(z_\alpha + z_\beta\right)^2\left(\sigma^2\right)}{d^2}$$

Where σ = 1.3, The max SD of modified Rankin Score among various groups of TBM

d = 50% of mean MRS score of groups having maximum variation (=1.3), the difference considered to be statistically significant

(Ref. RAJENDRAN, Santhosh et al. Outcomes of patients presenting with central nervous system tuberculosis at a tertiary care center in India. International Journal of Community Medicine and Public Health, [S.l.], v. 8, n. 1, p. 138-146, dec. 2020. ISSN 2394-6040.)

Design effect k = 2 for considering multiple within groups

type I error α = 5% corresponding to 95% confidence level

type II error β = 10% for detecting results with 90% power of study

Data loss factor = 10%

So, the required sample size is calculated to be

***n* = 117**

Each group will have 39 patients i.e group A ,B and C will have 39 patients each.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean and SD. Qualitative variables were compared using Chi-Square test /Fisher's exact test as appropriate. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 23.0.

RESULTS

Table 1: System wise distribution of ADRs after initiation of the therapeutic regimen.

System	ADR	No of ADR (%)	ADR in each system [out of 87] (%)	Incidence of ADR out of 70 patients (%)
GIT	Nausea & Vomiting	17(19.54)	33.33	41.43
	Gastritis	6(6.89)		
	Constipation	4(4.59)		
	Diarrhoea	2(2.29)		
Hepato-biliary	Hepatitis	11(12.64)	12.64	15.71
CNS	Headache	5(5.74)	14.94	18.57
	Giddiness	4(4.59)		
	Confusion	2(2.29)		
	Anxiety	1(1.14)		
	Irrelevant talks	1(1.14)		
PNS	Peripheral neuropathy	9(10.34)	10.34	12.85
Skin	Rash	7(8.04)	8.04	10
Renal	Dysuria	2(2.29)	2.29	2.85
Endocrine	Hypothyroidism	2(2.29)	2.29	2.85
Musculoskeletal	Arthralgia	3(3.54)	3.54	4.28
Metabolic	Hyperuricemia	3(3.54)	5.74	4.28
	Hyperglycemia	2(2.20)		2.85
Ophthalmic	Vision impairment	4(4.59)	4.59	5.71
Oto Vestibular	Tinnitus	2(2.29)	2.29	2.85

Table showing contribution to the total pool out of 87 ADR that developed and incidence in 70 patients.

33.17% ADR seen related to GIT, next CNS with 14.94%, Hepato billiary 12.64%, PNS 10.39%, Skin 8.04%, Metabolic disorders 5.74%, Ophthalmic 4.59%, Musculoskeletal 3.54% and Renal, Endocrine and Oto vestibular each 2.29%.

Nausea and Vomiting is the single most common ADR(19.54%) followed by Hepatitis 12.64% and Peripheral neuropathy with 10.39%.

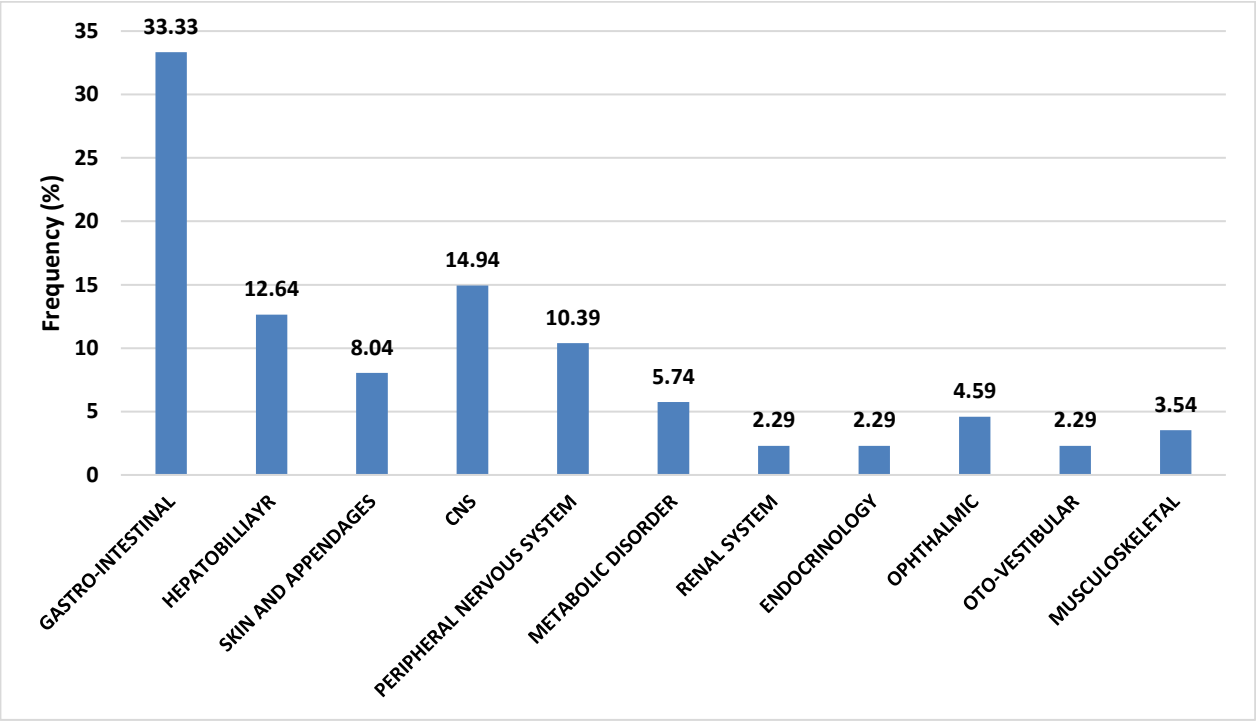

Figure 1: Distribution of system wise ADRs

Table 2: Total distribution of individual ADRs in our study

Adverse Drug Reactions	Groups						p value
	A		B		C		
	N	%	N	%	N	%	
Nausea &vomiting	4	10.30%	2	5.10%	11	28.20%	**0.010**
Gastritis	3	7.70%	2	5.10%	1	2.60%	0.590
Constipation	0	0.00%	2	5.10%	2	5.10%	0.355
Diarrhoea	0	0.00%	2	5.10%	0	0.00%	0.131
Hepatitis	0	0.00%	5	12.80%	6	15.40%	**0.045**
Rash	2	5.10%	3	7.70%	2	5.10%	0.859
Hypothyroidism	0	0.00%	2	5.10%	0	0.00%	0.131
Anxiety	0	0.00%	0	0.00%	1	2.60%	0.365
Irrelevant talk	0	0.00%	1	2.60%	0	0.00%	0.365
Headache	3	7.70%	2	5.10%	0	0.00%	0.232
Giddiness	1	2.60%	1	2.60%	2	5.10%	0.772
Confusion	1	2.60%	1	2.60%	0	0.00%	0.601
Dysuria	0	0.00%	1	2.60%	1	2.60%	0.601
Hyperuricemia	2	5.10%	0	0.00%	1	2.60%	0.358
Vision impairment	1	2.60%	1	2.60%	2	5.10%	0.772
Peripheral neuropathy	3	7.70%	2	5.10%	4	10.30%	0.697
Arthralgia	2	5.10%	1	2.60%	0	0.00%	0.358
Tinnitus	1	2.60%	0	0.00%	1	2.60%	0.601
Hyperglycemia	0	0.00%	1	2.60%	1	2.60%	0.601

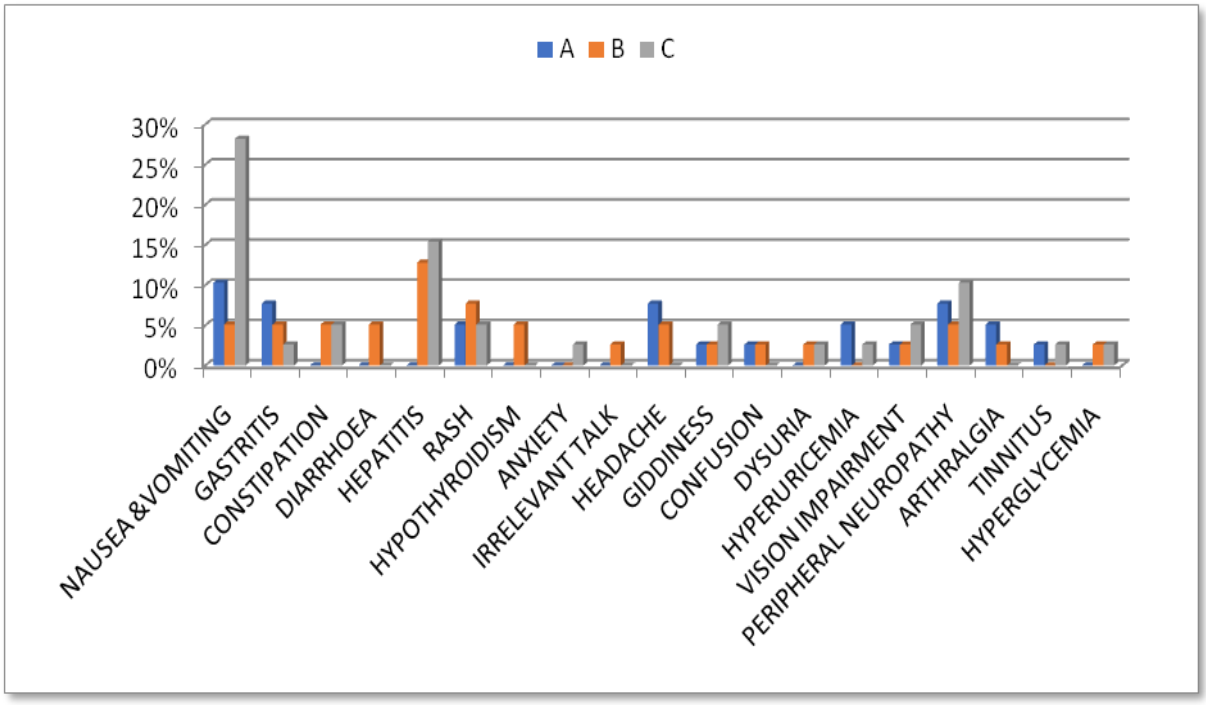

Figure 2

Table 3: First set of ADRs developed in our study i.e ADR1

ADR1	Group					
	A		B		C	
	N	%	N	%	N	%
Anxiety	0	.0%	0	.0%	1	2.6%
Arthralgia	2	5.1%	1	2.6%	0	.0%
Confusion	1	2.6%	1	2.6%	0	.0%
Constipation	0	.0%	2	5.1%	1	2.6%
Diarrhoea	0	.0%	2	5.1%	0	.0%
Gastritis	1	2.6%	1	2.6%	1	2.6%
Giddiness	1	2.6%	1	2.6%	1	2.6%
Headache	2	5.1%	2	5.1%	0	.0%
Hepatitis	0	.0%	3	7.7%	5	12.8%
Hyperglycemia	0	.0%	1	2.6%	1	2.6%
Hypothyroidism	0	.0%	2	5.1%	0	.0%
Irrelevant talk	0	.0%	1	2.6%	0	.0%
Nausea vomiting	4	10.3%	2	5.1%	10	25.6%
Nil	21	53.8%	15	38.5%	11	28.2%
Peripheral neuropathy	3	7.7%	2	5.1%	4	10.3%
Rashes	2	5.1%	2	5.1%	2	5.1%
Tinnitus	1	2.6%	0	.0%	1	2.6%
Vision impairment	1	2.6%	1	2.6%	1	2.6%
Total	39	100.0%	39	100.0%	39	100.0%

Table 4: Causality assessment of first set of ADR (ADR1) using WHO-UMC scale.

WHOUMC causality assessment score 1	Group					
	A		B		C	
	N	%	N	%	N	%
NIL	21	53.8%	15	38.5%	11	28.2%
POSSIBLE	9	23.1%	12	30.8%	12	30.8%
PROBABLE	7	17.9%	7	17.9%	11	28.2%
UNCLASSIFIED	0	.0%	0	.0%	2	5.1%
UNLIKELY	2	5.1%	5	12.8%	3	7.7%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.234

Above table shows the frequency distribution and association of WHO UMC causality assessment score 1 of the study subjects according to the groups. Group A consist of 23.1% possible, 17.9% probable, 5.1% unlikely and 53.8% nil; group B consist of 30.8% possible, 17.9% probable, 12.8% unlikely and 38.5% nil while group C consist of 30.8% possible, 28.2% probable, 5.1% unclassified, 7.7% unlikely and 28.2% nil.

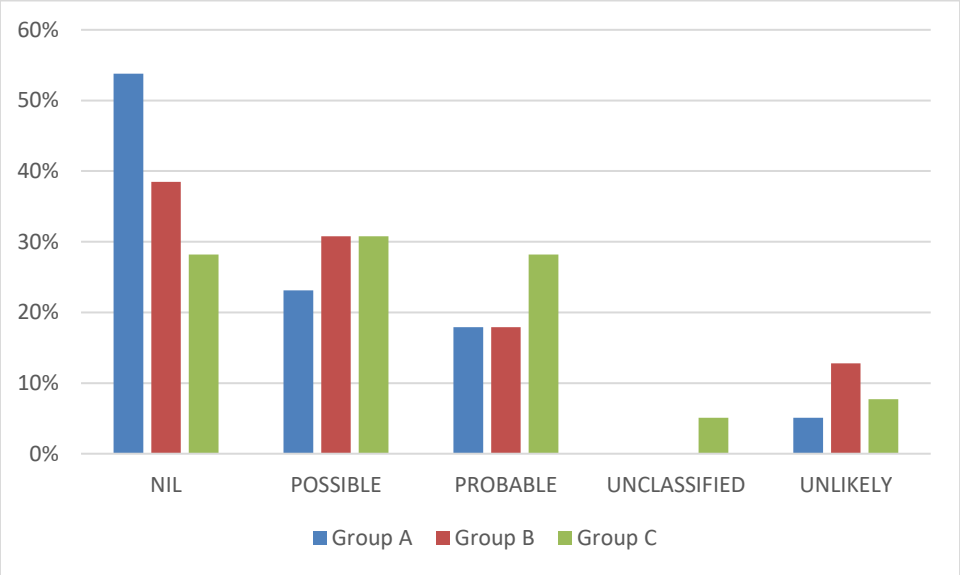

Figure-3

Table 5: Severity assessment of ADR 1 using Hartwig Siegel scale

Hartwing severity index 1	Group					
	A		B		C	
	N	%	N	%	N	%
Mild	13	33.3%	17	43.6%	19	48.7%
Moderate	5	12.8%	7	17.9%	9	23.1%
Nil	21	53.8%	15	38.5%	11	28.2%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.238

Above table shows the frequency distribution and association of Hartwig severity index 1 of the study subjects according to the groups. Group A consist of 33.3% mild, 12.8% moderate and 53.8% nil; group B consist of 43.6% mild, 17.9 moderate and 38.5% nil while group C consist of 48.7% mild, 23.1% moderate and 28.2% nil.

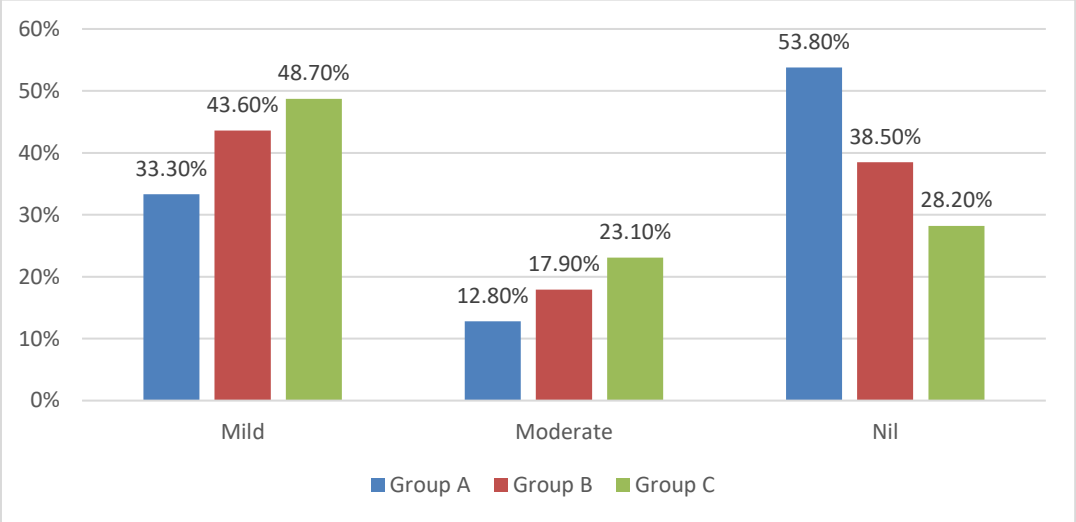

Figure 4

Table 6: Distribution of Second set of ADRs developed i.e ADR2

ADR 2	Group					
	A		B		C	
	N	%	N	%	N	%
Constipation	0	.0%	0	.0%	1	2.6%
Dysuria	0	.0%	1	2.6%	1	2.6%
Gastritis	2	5.1%	1	2.6%	0	.0%
Giddiness	0	.0%	0	.0%	1	2.6%
Headache	1	2.6%	0	.0%	0	.0%
Hepatitis	0	.0%	2	5.1%	1	2.6%
Hyperuricemia	2	5.1%	0	.0%	1	2.6%
Nausea &vomiting	0	.0%	0	.0%	1	2.6%
Nil	34	87.2%	34	87.2%	32	82.1%
Rash	0	.0%	1	2.6%	0	.0%
Vision impairment	0	.0%	0	.0%	1	2.6%
Total	39	100.0%	39	100.0%	39	100.0%

Table 7: Causality assessment of ADR2 using WHO-UMC scale

WHOUMC causality assessment score 2	**Group**					
	A		**B**		**C**	
	N	**%**	**N**	**%**	**N**	**%**
Possible	3	7.7%	2	5.1%	4	10.3%
Probable	2	5.1%	3	7.7%	3	7.7%
Nil	34	87.2%	34	87.2%	32	82.1%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.910

Above table shows the frequency distribution and association of WHO UMC causality assessment score 2of the study subjects according to the groups. Group A consist of 7.7% possible, 5.1% probable and 87.2% nil; group B consist of 5.1% possible, 7.7% probable and 87.2% nil while group C consist of 10.3% possible, 7.7% probable and 82.1% nil.

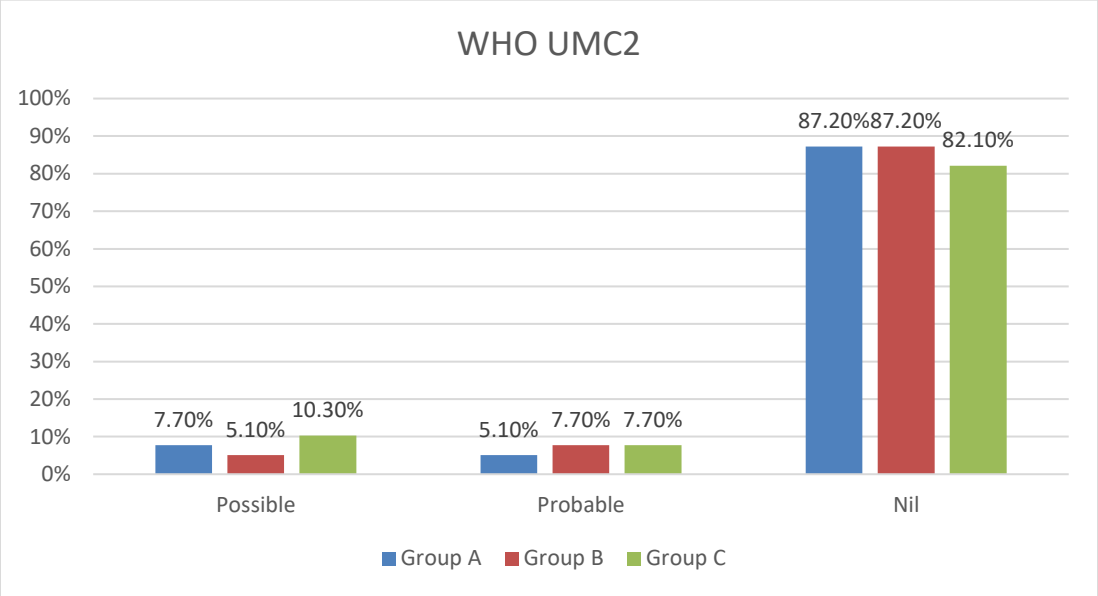

Figure 5

Table 7: Severity assessment of second set of adverse reactions i.e ADR2 using Hartwig Siegel scale

Hartwig severity index 2	Group					
	A		B		C	
	N	%	N	%	N	%
Mild	4	10.3%	5	12.8%	2	5.1%
Moderate	1	2.6%	0	.0%	5	12.8%
Nil	34	87.2%	34	87.2%	32	82.1%
Total	39	100.0%	39	100.0%	39	100.0%

Applied χ^2 test for significance. p value = 0.079

Above table shows the frequency distribution and association of Hartwig severity index 2of the study subjects according to the groups. Group A consist of 10.3% mild, 2.6% moderate and 87.2% Nil; group B consist of 12.8% mild and 87.2% Nil while group C consist of 5.1% mild, 12.8% moderate and 82.1% Nil.

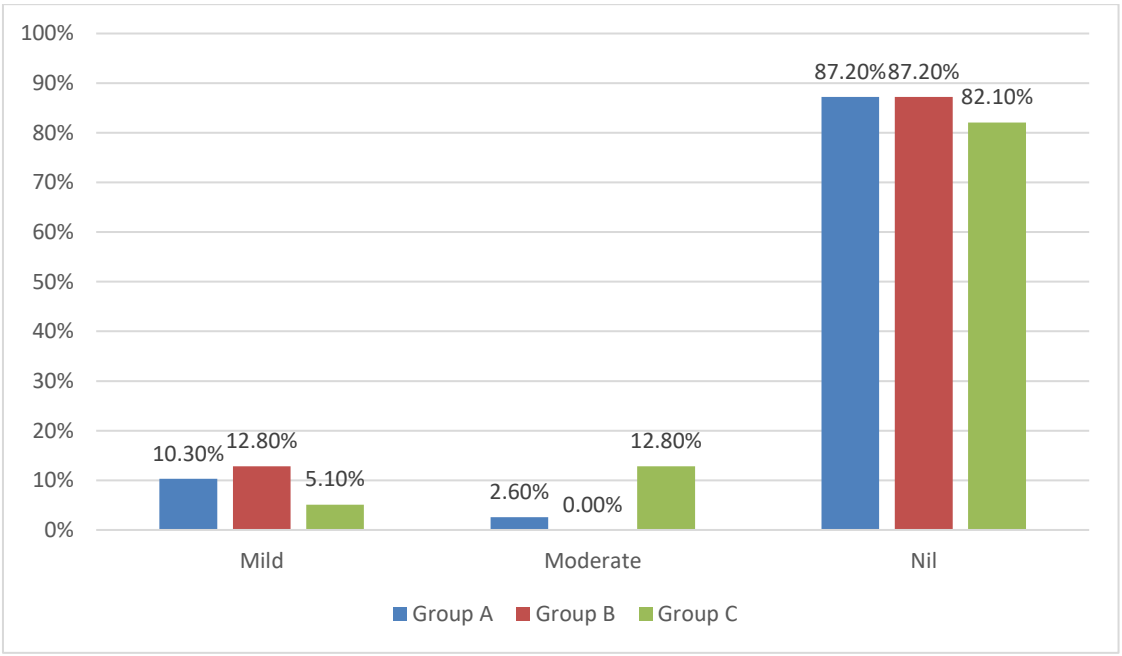

Figure 6

DISCUSSION

The present study was conducted from October 2021 to September 2022 at Department of Pharmacology in collaboration with Department of Neurology and Department of Respiratory medicine, KGMU, Lucknow. 117 patients who met inclusion criteria were studied during these one-year time frame.

In our study 58.97% comprised of male and female 41.03% this goes in tune with study conducted by **H K Anuradha et al**[15] where it has been shown that 59% were male and 41% were male. Similarly study conducted by **Verajit Chotmongkol et al**[16] found 55.6% male and 44.4% female. Similarly **Chia Peck Kee et al**[17] found 60.7% male whereas female constituted 39.3%. 60% males were also found in the study conducted by **Emily E. Evans et al**[5]**.** Most common presenting age found was 18 to 30 years which is similar to study conducted by **L Mathukumalli N et al**[18] where 56.5% were of the same age group similar to the finding by **Stephen Kent et al**[19]**.**

Maximum population in all the group were from rural background compared to urban population,69.2%, 76.9%, and 79.5% respectively in group A, B and C. This can be attributed due to lack of awareness, poverty, nutrition issues and lack of easy accessibility to better health facilities. It is similar to the finding by **Abdul Majid Wani et al**[20] where study in Kashmir valley shown 76.3% TBM cases were from rural areas.

Maximum Prevalence of TBM was found in those engaged in daily wage labour. These migrants laborers who lived in poor socioeconomic condition, undernutrition, overcrowding and lack of easy accessibility to better health could be attributed for the finding. Work done by **Priyanka Sharma et al**[21] also is in the same tune where daily wage workers constituted a majority of the patients. **World health organization**[22] in its guidelines also emphasized the need of prevention of the disease in migrant laborers because of vulnerability of this group for developing infection. 89.7% in group A, 82.1% in group in group B, and 76.9% in group C had no past history of pulmonary TB which implies that there may be extrapulmonary causes to tuberculous meningitis in addition to most commonly thought pulmonary origin. It is in the same tune with findings demonstrated by **Amrut Savadkar et al**[23]**.**

Total 87 adverse drugs reactions (ADRs) were observed in 67 patients. Since ATT along with dexamethasone (constituent of our therapeutic regimen) are well known for developing wide spectrum of adverse reactions. Causality assessment and severity assessment also done using WHO –UMC scale and Hartwig scale. System wise contribution to ADR pool and Incidence ADRs were noted.

Gastro Intestinal adverse drug reactions

Contribution of GI ADRs in our study 33.33% while incidence in 70 patients found to be 41.43%. Similar to our study, **Athira et al**[24] in a study conducted in Kerala reported incidence of GI symptoms to be 38.04%. **Kumarjit Sinha et al**[25] in a work done in Manipur reported 53.52% incidence of ADRs related to gastro intestinal system. In contrast to our finding **Anusha et al**[26] and **Shinde et al**[27] reported the incidence to be 70.84% and 12.5% respectively.GI irritant nature of ATT drugs appears to be the cause leading to majority of GI symptoms. Nausea and vomiting found to be significant in our study with 28.2% patients of group C experiencing it.

Hepato billiary adverse drug reactions

Hepatotoxicity is the 1.5 fold increased in the alanine transaminase level (ALT) compared to the level before treatment. Generally, hepatobilliary adverse reactions manifest fully after 3 weeks of ATT. Incidence of hepatitis in our study was noted to be 15.71%. This goes in sync with study conducted by **Kumarjit Sinha et al**[25] where incidence of ATT induced hepatitis came to be 15.49%.In same note **Athira et al**[24] reported the incidence of 14.28% hepatitis. However worker like **Anusha et al**[26] noted ATT induced hepatitis in 57.14% of Nepalese patients. ATT induced hepatotoxicity as per the literatures is due to formation or reduced elimination of toxic metabolites. Pyrazinamide is the most hepatotoxic drug[28]. Although incidence of isoniazid induced hepatitis is reported less its hepatotoxicity is enhanced by rifampicin[29] .Variations seen in the incidence of ATT induced hepatitis is attributed to the habit of alcohol or history of intake of herbal medicine which is common in patients with poor socio economical background.

Peripheral Nervous system adverse drug reaction

The incidence of peripheral neuropathy in our study found to be 12.85%.Study conducted by **Anupa Khattri Chettri et al**[30] noted peripheral neuropathy in 20% patients. Whereas work done by **Koju et al**[31] and **Shinde et al**[27] reported incidence of 18.57% and 5.04% respectively. INH and very rarely Ethambutol are held responsible for ATT induced peripheral neuropathy. Variation in different studies might be due to prophylactic pyridoxine therapy with ATT.

Metabolic adverse drug reactions

1. Hyperuricemia-In our study incidence of Hyperuricemia was found to be 4.28%. Pyrazinamide and ethambutol are the two most important ATT reported to cause hyperuricemia. Our finding goes in the same tune with finding of **Gurprit Singh Nanda et al**[32] where 3.2% hyperuricemia was reported. In contrast **Athira et al** reported only 1.90% incidence of hyperuricemia.
2. Hyperglycemia-2.85% is the incidence of hyperglycemia reported in our study. Corticosteroid given with ATT as a treatment regimen in TBM appears to be the cause. In contrast to our finding **Gholami et al**[33] found 8.7% incidence of hyperglycemia while **Gulbay et al** [34]reported.

Skin adverse drug reactions

The incidence of cutaneous reaction in the form of rashes has been found 10.0% in our study. Rashes were reported generally after two weeks of the therapy. This finding goes in similar tune with the studies conducted by **Kumarjit Sinha et al**[35] and **Gurprit Singh Nanda et al** [32]where incidence of rashes noted to be 8.45% and 8.8% respectively. The most common cause of ATT induced rash is attributed to pyrazinamide, followed by ethambutol and rifampicin[36]

Musculoskeletal adverse drug reaction

Frequency of musculoskeletal ADR in the form of arthralgia noted to be 4.28%.it usually occurred in a range of 1 to 6 month in our patients and found to be associated with hyperuricemia. **Sachin Tutu et al**[14] found arthralgia incidence of 7.46% in work done at KGMU, Lucknow, whereas In contrast to our study, **Dhingra et al**[37] reported incidence of 35% .

Renal system adverse drug reaction

Incidence of Dysuria reported in our study came out to be 2.85%. Aminoglycosides may produce toxic effect accumulating in renal tubules. Similar to our finding **Verma et al** [27]reported 2.22% while **Sachin Tutu et al**[14] reported dysuria incidence of 4.48%.

Endocrine adverse drug reactions

Tuberculous meningitis can produce hypothalamic pituitary because of different pathological mechanism which can manifest into various hormonal imbalance[38–41]. ATT drug especially rifampicin is believed to cause hypothyroidism as it is CYP450 enzyme inducer leading to increased hepatic metabolism of T4 [42–44] In our study incidence of 2.85% hypothyroidism is reported. In contrast, a study done by **Surendra Menon et al**[45] in 60 patients taking ATT drugs reported 63.3% patient that developed hypothyroidism.

Ophthalmic adverse drug reaction

TBM also leads to vision impairment by papilledema, tuberculoma of optic chiasma, optic tract compression and pressure effects[46–48].In our study incidence of vision impairment noted as 5.71% which is similar to study conducted by **Sivaraj et al**[49] and **Maciel et al** [50]which is 4% and 4.44% respectively.Ethambutol can cause retrobulbar neuritis if receiving dose more than 35mg/kg/day[51,52]

Oto vestibular adverse drug reactions

In our study, oto vestibular adverse effects in the form of tinnitus observed with incidence of 2.85 %.TBM with its wide spectrum of pathology can also give rise to this disorder[53,54].Aminglycoside can also induce various tympano vestibular impairments[55,56].In similarly line **Sivaraj et al**[49] reported 2% incidence of tinnitus

In TBM interruption of the drug therapy is an independent risk factor for death[4,57,58] so rechallenge and dechallenge couldn't be performed. Various disorders like hypothyroidism, ocular and auditory disorders might develop due to disease per se. Therefore, while assessing causality majority of the disorders were categorized as "possible".

23.1% in group A, 30.8% in each group B and C falls under the possible category of WHO-UMC causality assessment scale. None of the ADR fell under definite .Similar finding of 87.5% possible was reported by **Anusha et al**[59]**.** While assessing severity of ADRs using Hartwig & Siegel scale, we found moderate severity in 12.8% group A, 17.8% in group B and 23.1% group C while majority of the ADRs were of mild grade. No any severe ADR on the scale noted. Work done by **Anupa et al**[30] also noted similar observation where majority (93.3%) cases were mild compared to moderate scale in Hartwig Siegel severity scale. Based on these finding it appears that the present therapeutic regimen is relatively safe and no change or interruption is needed so far ADR is concerned.

CONCLUSION

- Out of 117 patients, male (58.97%) constituted more as compared to females.
- Age group of 18 to 30 yrs was most vulnerable except in TBM with hydrocephalus where 51 to 60 yrs age group found to be more susceptible due immunological factors and co morbidities.
- Prevalence of TBM found more in rural population because of lack of awareness and delay in diagnosis and treatment as access to better health facilities is difficult.
- Daily wage workers found to be more vulnerable because of lack of education, poverty, malnourishment and access to better health facilities
- Maximum number of patients developing ADR reported with GIT symptoms reflecting the fact that ATT drugs irritate GIT of maximum patients
- Hepatitis also seen in maximum patients indicating the role of monitoring of LFT during the therapy.
- On assessment of causality through WHO UMC scale, maximum adverse drug reaction has been categorized under "possible" followed by category of "probable" suggesting that due to lack of dechallenging in the rechallenging, in the process of causality assessment none of the ADR could be grouped under "definite"'
- While assessing severity of ADR through Hartwig scale, maximum ADR were "mild" reflecting that for bigger proportion of ADRs reported, no change in or interruption in the current standard therapeutic regimen is needed.

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