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WEIGHT BASED ANTI TUBERCULAR THERAPY V/S HIGH DOSE ANTI TUBERCULAR THERAPY

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Abstract: Tuberculosis is a highly contagious disease caused due to *Mycobacterium tuberculosis* infection. Though the methods of treatment of the disease have been standardized since long, many people, especially in the developing countries, still succumb to it. According to recent statistical figures published by the World Health Organization (WHO), 10.4 million new cases of TB were reported worldwide in the year 2015 alone. Here we presented a case of 30-year-old female patient was brought to casualty with history of 5 episodes of generalized tonic-clonic seizures since morning. There was no postictal confusion. These complaints were associated with headache and nausea. There was no history of fever, blurring of vision, diplopia or altered sensorium. There was no history of trauma or similar episodes in the past. Patient is a known case of pulmonary tuberculosis, and has received anti tubercular therapy for 6 months, 7 years ago. Low concentrations of anti-TB drugs should be dealt with extreme caution as it may influence the pathogen's drug susceptibility and the short-course treatment strategy for fighting TB. A better and easier way to overcome low serum concentrations of anti-TB drugs is to prescribe high doses for TB treatment, subject to prior verification of absence of adverse effects and cross drug resistance. Taking also into account the increase in adverse effects and the host/bacterial factors, It is becoming a critical point to identify if those patients in whom high-dose treatments are truly cost-effective.

INTRODUCTION

Tuberculosis is a highly contagious disease caused due to *Mycobacterium tuberculosis* infection. Though the methods of treatment of the disease have been standardized since long, many people, especially in the developing countries, still succumb to it. According to recent statistical figures published by the World Health Organization (WHO) [1, 10.4 million new cases of TB were reported worldwide in the year 2015 alone.

It was also observed that while 1.4 million died of the disease in the same year, an estimated 480,000 were diagnosed with multidrug-resistant TB [MDR-TB, defined as resistant to at least isoniazid (INH) and rifampin (RFP)] and an additional 100,000 with rifampicin-resistant

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TB (RR-TB). Since the standard treatment regimens are ineffective in the treatment of such patients, they were compelled to undertake the MDR-TB specific treatment.

Hence, it is proposed that the advent and worldwide distribution of newanti-TB drugs (MDR-TB drugs) is indispensable for winning the war against TB on a global level. Interestingly, it was observed that over 95% of the total number of TB associated fatality cases recorded in 2015 occurred in low- and middle-income countries. This points towards the need of improving the standards of medical care and accessibility to traditional as well as contemporary (MDR) anti-TB drugs, which can be achieved by lowering the prices and maintaining consistent supplies.

However, the process of development of new (MDR) anti-TB drugs that has improved efficacy and safety is still under experimentation. The only option to control the situation presently is to devise new methods that can help in deriving maximum benefits from traditionally available therapeutic agents. Dosage optimization of existing medication regimens is one such method that can improve the efficacy of the anti-TB drugs.

CASE PRESENTATION

A 30-year-old female patient was brought to casualty with history of 5 episodes of generalized tonic-clonic seizures since morning. There was no post-ictal confusion
These complaints were associated with headache and nausea.
There was no history of fever, blurring of vision, diplopia or altered sensorium
There was no history of trauma or similar episodes in the past.
Patient is a known case of pulmonary tuberculosis, and has received anti tubercular therapy for 6 months, 7 years ago.
On examination:
Pulse- 110/min
Blood pressure – 100/70 mmHg
Oxygen saturation – 98% on room air
Neck rigidity +
No focal neurological deficits noted.

Investigations during hospital stay are as follows:

Hemoglobin	9.6
Total leukocyte count	8,600
Platelets	3,44,000
RFT	normal
LFT	normal
INR	1.06
ESR	97
HIV/Hbsag/HCV	Non reactive
Urine examination	Normal

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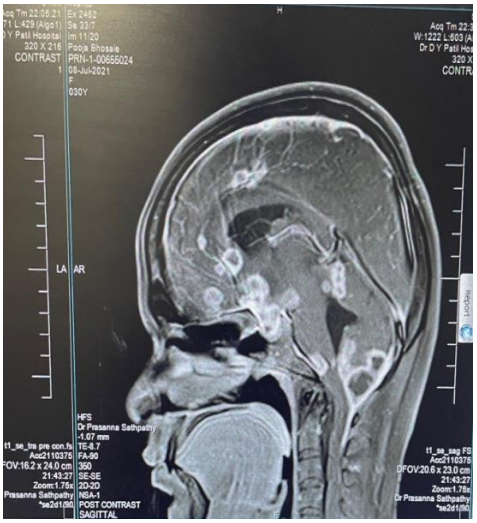
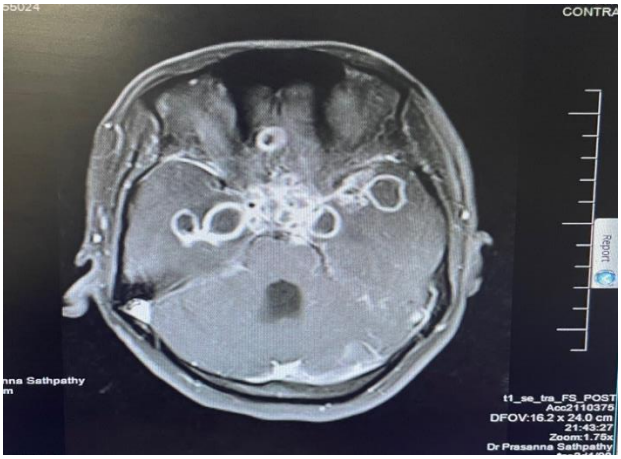
CT Brain on admission:
Early communicating hydrocephalus with peri ventricular ooze, effacement of basal cisterns, suggestive of raised intra cranial tension suspicion of ring enhancing lesions in basal cisterns and left ganglio-capsular and left temporal and bilateral frontal areas.

Cerebrospinal fluid examination:
Proteins- 660.
CBNAAT- POSITIVE
TLC- 126 (90% lymphocytes)
ADA- negative
MRI Brain with contrast:
Suggestive of disseminated tuberculoma with tubercular meningitis
Communicating hydrocephalus.





Patient was started on standard anti tubercular therapy (HRZE regimen) according to her weight (40kg)and discharged after 72 hours of observation in the hospital. She was on regular follow up

2 months after starting Anti Tubercular Therapy, patient presented back to casualty with complaints of 3 episodes of generalized tonic-clonic seizures, same as previous.
She was admitted for further work up and in view of drug resistance to standard anti tubercular therapy.

A repeat MRI with contrast study was done:
There was no significant change in the number or size of lesions in comparison to the previous scan.

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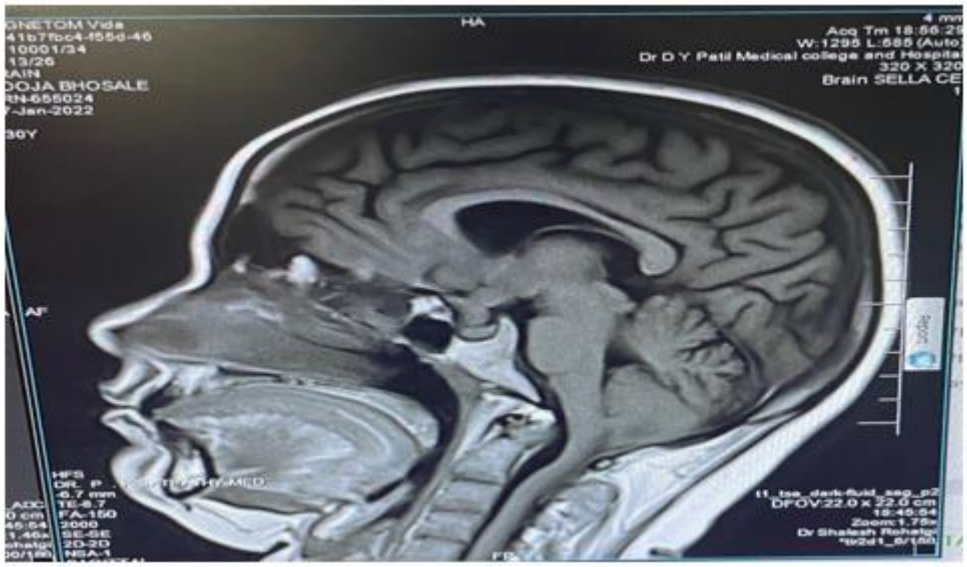
Communicating hydrocephalus +

Under all aseptic conditions, a brain biopsy was done and was sent for histo-pathological examination and line probe assay studies, which confirmed the diagnosis of Central Nervous System Tuberculomas sensitive to Rifampicin and Isoniazid.

Patient was then started on high dose anti tubercular therapy and discharged after 72 hours of starting treatment and was advised regular weekly to follow-up.

6 months post high dose anti tubercular therapy, a repeat MRI brain with contrast study was done to check for response to the treatment:



There was complete remission of the lesions on the repeat studies. Patient has clinically improved, with good tolerance to high dose anti tubercular therapy.

DISCUSSION

In many parts of the world, tuberculosis (TB) is regarded as one of the most serious threats to public health. The threat is exacerbated in developing countries due to a lack of advanced medical facilities and modern anti-TB drugs.[5] In such cases, it appears that dosage optimization of existing medication regimens is the only viable option. The results of a therapeutic drug monitoring study indicate that high-dose treatment regimens can compensate for low serum concentrations of anti-TB drugs and shorten therapy duration.[6]

Differences in host body weight, metabolic processing of the drug, malabsorption, and/or drug-drug interaction are some of the most common causes of low anti-TB drug concentrations in the serum.[7] Furthermore, the drugs' inability to reach the cavitary pulmonary and extra pulmonary tissues contributes to their therapeutic inefficiency. In such cases, higher doses can help compensate for the pathogenic effects of pathogen enhancements such as physical barriers, efflux pumps, and genetic mutations.[8]

The WHO has already reviewed and written into the guidelines the required drug concentrations of a highly effective TB therapy [2-4]. The most widely accepted standards for

determining anti-TB drug dosage are based on WHOM recommendations [4]. Table 1 summarises the recommended drug concentrations for TB treatment based on WHO guidelines. Despite the fact that the regimens recommended based on these values are sometimes considered lengthy and complex, they have been found to be highly effective in the majority of cases[9].

Drugs	WHO-recommended dose				Recommended high dose	
	Daily		Three times per week		Daily dose	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)	Dose and range (mg/kg body weight)	Maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900	16–18	
Rifampicin	10 (8–12)	600	10 (8–12)	600		900–1200
Pyrazinamide	25 (20–30)	–	35 (30–40)	–		
Ethambutol	15 (15–20)	–	30 (25–35)	–	25	
Streptomycin	15 (12–18)	[a]	15 (12–18)	1000		

Host nutritional status, bacterial cell wall as physical barrier, efflux pump actions, low rifampicin levels in csf than in plasma are some of the causes for low serum concentrations of anti-tubercular drug levels in the body.[10]

CONCLUSION

Therefore, in conclusion, low concentrations of anti-TB drugs should be dealt with extreme caution as it may influence the pathogen's drug susceptibility and the short-course treatment strategy for fighting TB. A better and easier way to overcome low serum concentrations of anti-TB drugs is to prescribe high doses for TB treatment, subject to prior verification of absence of adverse effects and cross drug resistance. Taking also into account the increase in adverse effects and the host/bacterial factors, It is becoming a critical point to identify if those patients in whom high-dose treatments are truly cost-effective.

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