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Original Article

Psychiatric disorders in patients with multidrug resistant tuberculosis (MDR-TB) in Sardjito Hospital, Yogyakarta, Indonesia

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Abstract

Introduction: Tuberculosis has become a chronic debilitating disease in developing countries, particularly after the emergence of multidrug resistant tuberculosis (MDR-TB). Second line treatments for the disease which were subsequently developed were associated with psychiatric disorders among patients. Psychiatric disorder can either be induced by treatment regiments or psychosocial factors. Cycloserine administration is frequently reported to be associated with psychiatric disorders. In this study, we examined the prevalence and characteristics of psychiatric disorders among MDR-TB patients in Sardjito Hospital, Yogyakarta, Indonesia.

Methods: In this descriptive study, we studied medical records of MDR-TB patients admitted for MDR-TB treatments to Sardjito Hospital from January 2014 to July 2016 and screened for psychiatric disorders.

Results: We found that 32.8% of the patients had psychiatric disorders, some of which had multiple psychiatric diagnoses (14.1%). The diagnoses were medication induced delirium, substance/medication induced psychotic disorder, substance/medication use depressive disorder, depressive type schizoaffective disorder, bipolar I disorder current episode severe manic with psychotic features, mild depression, moderate depression, major depression without psychotic features, major depression with psychotic features, adjustment disorders with mixed anxiety and depressed mood, adjustment disorder with anxiety, acute stress disorder, and insomnia. Psychiatric disorders were significantly associated with cycloserine dose and sex. Psychotic symptoms were significantly associated with sex and level of education.

Conclusion: The presence of psychiatric disorders might disturb MDR-TB treatment resulting in poor outcomes. Precaution and prompt managements are required for psychiatric disorders in patients receiving MDR-TB treatment regiments.

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Introduction

Tuberculosis is a chronic respiratory infection caused by Mycobacterium tuberculosis and is a major global public health concern in developing countries.[1,2] The discovery of anti-tuberculosis drugs had provided hope for tuberculosis eradication. Tragically, in the last 25 years, the misuse of these drugs has resulted in drug resistant tuberculosis. Drug resistance arises due to the improper use of antibiotics in chemotherapy of drug susceptible tuberculosis patients such as administration of improper treatment regimens by health care workers and failure to ensure that patients complete the whole course of the treatment.[3-5]

Psychiatric issues present a challenge in the management of patients with multidrug resistant tuberculosis (MDR-TB). Psychiatric disorders can either be complications related to anti-tuberculosis drugs or induced by psychosocial factors. Both require aggressive

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management.[6,7] Psychiatric symptoms induced by anti-tuberculosis medications used in MDR-TB therapies are well known. Psychiatric morbidity in tuberculosis patients were recognized as the cause of poor compliance, and increased morbidity and mortality from the disease. Thus, treating psychiatric problems in patients with tuberculosis may substantially improve treatment adherence and prognosis.[1,2,6,8]

The MDR-TB regiment is frequently reported to be associated with psychiatric disorders, particularly psychotic symptoms is cycloserine. Cycloserine is distributed throughout body fluids and tissues. There is no appreciable blood brain barrier to the drug, and cerebrospinal fluid (CSF) concentrations are approximately the same as those in plasma.[2] Symptoms usually appear within the first 2 weeks of therapy and disappear when the drug is withdrawn. The central manifestations include somnolence, headache, tremor, dysarthria, vertigo, confusion, nervousness, irritability, psychotic symptoms, suicide ideation, paranoid, catatonic and depressed reactions, twitching, ankle clonus, hyperreflexia, visual disturbances, paresis, and tonic-clonic or absence seizures.[8–12]

The inward treatment facility for MDR-TB in Sardjito Hospital, Yogyakarta, Indonesia was established in 2014. This facility has provided us a unique opportunity to observe psychiatric disorders and symptoms in patients treated for MDR-TB that will most likely be misdiagnosed in the outpatient settings. In this study, we examined medical records of patients admitted to Sardjito Hospital for MDR-TB treatments and screened for psychiatric disorders.

Methods

This study was a descriptive analytic study. We examined all medical records of patients admitted to MDR-TB ward in Sardjito Hospital from January 2014 to July 2016. Only patients admitted for MDR-TB treatments were included in this study. We extracted data of demographic characteristics, MDR-TB treatments, and the diagnosis of psychiatric disorder and presence of psychotic symptoms. Psychiatric diagnosis was established by psychiatrist through direct clinical interview with patients as recorded in the medical records.

The data was then tabulated and coded for statistical analyses. The statistical analyses were conducted using SPSS software (version X, IBM Corporation, Armonk, NY). The statistical significance was defined at $P < 0.05$.

Results

In this study we identified 64 patients with MDR-TB admitted to Sardjito Hospital. The demographic and clinical characteristics of the subjects are presented in table 1.

Table 1. Demographic and clinical characteristics of subjects

Variables	Value
Age (year) (mean ± SD)	46.34 ± 13.69
Body height	160.41 ± 7.96
Body weight	46.03 ± 10.00
Sex [n (%)]	40 (62.5)
Male	24 (37.5)
Female	
Marital status [n (%)]	
Single/divorced	16 (25.0)
Married	48 (75.0)
Occupational status [n (%)]	
Unemployed	6 (9.4)
Housewife	12 (18.8)
Labor	12 (18.8)
Student	2 (3.1)
Civil servant/retired	7 (10.9)
Farmer	1 (1.6)
Private workers	15 (23.4)
Merchant	1 (1.6)
Driver	2 (3.1)
Self employed	6 (9.4)
Education [n (%)]	
No formal education	5 (7.8)
Elementary school	10 (15.6)
Junior high school	13 (20.3)
Senior high school	25 (39.1)
Bachelor/strata degree	11 (17.2)
Psychiatric diagnoses [n (%)]	
Non	43 (67.2)
Single	12 (18.8)
Multiple	9 (14.1)
Psychotic symptoms [n (%)]	
Present	11 (52.4)
Absent	10 (47.6)

SD: Standard deviation

Table 2. Association between age, height, weight, and cycloserine dose with psychiatric disorders

Psychiatric disorders		Mean ± SD	t-test		
			t	df	P
Cycloserine (mg)	Present	636.90 ± 246.55	2.339	62	0.023
	Absent	463.95 ± 291.36			
Age (year)	Present	46.67 ± 11.63	0.131	62	0.896
	Absent	46.19 ± 14.72			
Weight (kg)	Present	44.86 ± 9.98	-0.665	62	0.509
	Absent	46.67 ± 10.08			
Height (cm)	Present	157.53 ± 8.03	-1.839	62	0.074
	Absent	162.21 ± 7.54			

SD: Standard deviation; df: Degree of freedom

There were 21 patients (32.8%) who were diagnosed with psychiatric disorders, some of which had multiple psychiatric diagnoses (n = 9, 14.1%). The diagnoses were medication induced delirium (n = 1), substance/medication induced psychotic disorder (n = 6), substance/medication use depressive disorder (n = 2), depressive type schizoaffective disorder (n = 1), bipolar I disorder current episode severe manic with psychotic features (n = 1), mild depression (n = 1), moderate depression (n = 4), major depression without psychotic features (n = 1), major depression with psychotic features (n = 2), adjustment disorders with mixed anxiety and depressed mood (n = 1), adjustment disorder with anxiety (n = 7), acute stress disorder (n = 1), and insomnia (n = 4). History of previous psychiatric hospitalization (n = 1) and mild intellectual disability (n = 1) were also found among patients with psychiatric diagnoses.

The treatments for the psychiatric disorders varied. Three patients with adjustment disorder received only supportive psychotherapy and family psychoeducation. The antipsychotics prescribed were haloperidol (1-10 mg/day) and risperidone (4 mg/day). Some patients experienced extrapyramidal symptoms and were prescribed trihexyphenidyl (4 mg/day). The antidepressants were amitriptyline (50 mg/day) and fluoxetine (10-20 mg/day). Mood stabilizers prescribed for patient with manic episode was valproic acid (500 mg/day). The anti-anxieties prescribed were alprazolam (0.5-1 mg/day), lorazepam (1 mg/day), and clobazam (10 mg/day).

Cycloserine dose was associated with the presence of psychiatric disorders in our subjects. Subjects with psychiatric disorders were prescribed with higher doses of cycloserine (P = 0.023). Age, weight, and height were not associated with psychiatric disorders in MDR-TB patients (table 2).

We analyzed patient who had psychotic symptoms and found similar results. Patients who had psychotic symptoms were also prescribed with higher dose of cycloserine, although it was not statistically significant (P = 0.079). Age, weight, and height were not associated with psychotic symptoms in MDR-TB patients (Table 3).

Table 3. Association between age, height, weight, and cycloserine dose with psychotic symptoms

Psychotic symptoms		Mean ± SD	t-test		
			t	df	P
Cycloserine (mg)	Present	659.09 ± 306.65	1.785	62	0.079
	Absent	491.98 ± 277.64			
Age (year)	Present	48.00 ± 10.81	0.438	62	0.663
	Absent	46.00 ± 14.23			
Weight (kg)	Present	46.82 ± 12.37	0.286	62	0.776
	Absent	45.86 ± 9.54			
Height (cm)	Present	157.00 ± 9.59	-1.374	62	0.178
	Absent	161.29 ± 7.41			

SD: Standard deviation; df: Degree of freedom

Table 4. The association between sex, marital status, and level education with psychiatric disorders

Variables		Psychiatric disorders		Chi-square		
		Present	Absent	χ^2	df	P
Sex	Men	9	31	5.146	1	0.023
	Women	12	12			
Marital status	Single/divorced	5	11	0.024	1	0.878
	Married	16	32			
Level of education	Low	12	16	2.278	1	0.131
	High	9	27			

df: Degree of freedom

We further analyzed the association between sex, marital status, level of education with psychiatric disorders in MDR-TB patients. Patients who completed junior high school or lower were considered to have low level of education and those completed senior high school or higher were considered to have high level of education. We found that sex was associated with psychiatric disorders. The proportion of psychiatric disorders was significantly higher in women compared to men (P = 0.023). Marital status and level of education were not associated to psychiatric disorders (Table 4).

We further analyzed the association between sex, marital status, level of education, and psychotic symptoms in MDR-TB patients. We found that sex and level of education were significantly associated with psychotic symptoms. The proportion of psychotic symptoms were higher in women (P = 0.049) and in patients with low education (P = 0.033) (Table 5).

Discussion

The present study found that 32.8% MDR-TB patients admitted to Sardjito Hospital were diagnosed with psychiatric disorders and 52.4% of them had psychotic symptoms. Depression was the most common diagnosis. Psychiatric disorders and psychotics symptoms in MDR-TB patients are often associated with cycloserine administration. We found that significantly higher doses of cycloserine was administered in patients with psychiatric disorders but not in patients with psychotic symptoms. Psychiatric disorders and psychotic symptoms were more prevalent in women compared to men. Psychotic symptoms were also more prevalent in subjects with lower level of education.

Tuberculosis has been associated with psychiatric disorders, particularly depression, and this has been recognized as a cause of poor compliance and a cause of increased morbidity and mortality from the disease. The psychiatric morbidity reported in Sardjito Hospital was lower than previous report in India (69.28%).[1] Treating psychiatric disorders in patients with tuberculosis may substantially improve treatment adherence and the disease prognosis.

Similar to our finding, depression was also prevalent among MDR-TB patients in India.[1] Prolonged treatment and duration of the disease could cause helplessness in these patients. This problem is worsened by social stigma toward tuberculosis. These lead to the development of depression. The treatment for depression will improve the patient outcome. Antidepressant treatments can be maintained during MDR-TB treatment course.[13]

Table 5. The association between sex, marital status, and level education with psychotic symptoms

Variables		Psychotic symptoms		Chi-square		
		Present	Absent	χ^2	df	P
Sex	Men	4	36	3.871	1	0.049
	Women	7	17			
Marital status	Single/widow/divorced	2	14	0.329	1	0.566
	Married	9	39			
Level of education	Low	8	20	4.532	1	0.033
	High	3	33			

df: Degree of freedom

Psychiatric disorders are known adverse drug reactions of cycloserine. The possible neurobiological mechanisms may be binding to and modulation of N-methyl-D-aspartate receptor (NMDAR) antagonists and partial agonists at the NMDAR-associated glycine site,[5,14] as well as gamma-Aminobutyric acid (GABA) elevation due to inhibition of GABA transferase.[15] We found that higher cycloserine dose was associated with the presence of psychiatric disorders. It is recommended to reduce the dosage of cycloserine in order to observe less severe manifestations of cycloserine toxicity. Antipsychotics are very useful for managing neuropsychiatric effects and can be continued throughout the duration of MDR-TB treatments.[12]

Not only treatment regiments, but social factors, such as poverty, inadequate housing, and stigma are also significant determinants of psychiatric disorders in MDR-TB patients.[16] Stigma is one of the major concerns for MDR-TB patients. The impacts of stigma include social seclusion or rejection from family members, friends, neighbors, and/or health providers, internalized shame, financial instability, discrimination and its repercussion.[13]

Lower level of education is associated with poor and ineffective coping styles. This results in higher prevalence of psychiatric problems.[1] In this study, lower level of education was associated with higher risk for psychotic symptoms but not for the psychiatric disorders. Lower education was also associated with mal-compliance to treatment regiments and subsequent prolonged treatments.

Conclusion

In conclusion, psychiatric disorders are relatively common in patients who are being treated for MDR-TB. Cycloserine can directly affect central nervous system and induce psychiatric symptoms. Cautious observation for psychiatric symptoms should be regularly conducted for patients receiving cycloserine. It is very prudent for psychiatrists to be aware of psychiatric manifestations of second-line anti-tubercular drugs to improve patient compliance and outcomes through early diagnosis and treatment. We also recommend aggressive and prolonged treatment due to the frequency and occasional severity of the psychiatric effects of MDR-TB drugs.

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Authors' Contribution

Irwan Supriyanto developed the study design, extracted and analyzed the data, and drafted the manuscript. Sak Liung and Suprihatini collected and extracted data. Silas Henry Ismanto developed the study concept and supervised the study.

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Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

The protocol of this study had been approved by the Medical and Health Research Ethics Committee (MHREC) of the Medical Faculty, Universitas Gadjah Mada.

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