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Case Report

Influence social and healthcare support on psychiatric adverse events in MDR-TB patient

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Abstract

Introduction: Multidrug resistance tuberculosis (MDR-TB) is a continuing threat because the treatment is rather toxic. One of the causes of poor treatment outcome is due to the adverse events, especially the occurrence of psychiatric adverse events.
Methodology: The two cases presented in this paper are MDR-TB patients with psychiatric adverse events related to depression spectrum. The diagnosis of psychiatric adverse events was done by psychiatrist in the referral hospital.
Results: The treatment of MDR-TB and psychiatric adverse event was carried out simultaneously. One of the patients was able to manage the adverse events, but the other was not. The management of psychiatric adverse events need to be performed carefully. Social support of family and friends was received by the successful patient, while the other was not fully supported, thus failed the treatment.
Conclusion: The social support provided by the family and friends are precious for the successful treatment of MDR-TB psychiatric adverse events. The availability of healthcare personnel who is able to recognize the symptoms early is needed in the community healthcare service in order to properly detect and manage the psychiatric adverse events on MDR-TB patients.

Key words: psychiatric adverse events; multi-drug resistant tuberculosis patients; social support.

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Introduction

Multidrug resistance tuberculosis (MDR-TB), which defined as resistance to the two most effective first-line drug, both isoniazid and rifampicin [1]), is a continuing threat. Controlling Multidrugs Resistance Tuberculosis (MDR-TB) is a major concern for TB control program worldwide. MDR-TB requires longer treatment using second-line anti-TB drugs, which are more expensive and more toxic than the first-line anti-TB drugs [1,2]. Administration of anti-TB regimens having a longer duration and more drugs is feared to be a cause of more adverse events.. The adverse events reports on MDR-TB treatment has increased and known to be related to poor treatment outcome [3]. Zhang Y *et al.* (2017) reported that the number of successful treatment of MDR-TB reach only 52%. The high level of poor outcome consisted of died patients (9.4%), discontinued treatment (13.7%) and not evaluated (5.1%) [4]. World Health Organization (WHO) also reports the same situation: successful treatment MDR-TB is only 54% while global treatment success rate is 83%. [1].. This low level of successful treatment of MDR-TB surely will interfere the End TB Strategy program [5].

One of the causes of poor treatment outcome is due to the adverse events, so that special attention is required to observe the occurrence of the side effects in MDR-TB treatment. Zhang Y *et al.* recorded that almost all MDR-TB patients (90.7%) experienced at least 1 type of adverse event [4]. Meanwhile, WHO recorded a large number and various adverse event, starting from mild ones, such as nausea or vomiting, until severe ones, such as renal failure [6].

Beside these physical side effects, there were many reports of psychological side effects [7,8]. The attention on psychological side effects seems lower, differently bya physical adverse event that is usually directly delivered by the patient so to get immediate treatment as soon as possible. As far as psychological side effects are concerned, clinicians must be able to obtain enough information from the patients so that the side effects will not get worsen. Nevertheless, if this attention to psychological adverse events does not increase, it will affect the treatment outcome of MDR-TB.

The aim of this case series study is to show how management of psychological side effects is important in MDR-TB patients so it will not be neglected.

Case 1

A 25-yearold man, affected by pulmonary MDR-TB, started to take anti-MDR-TB drugs on March 22nd 2014 in Moewardi hospital, a regional referral hospital. He received Kanamycin 1000 mg, Levofloxacin 750 mg, Cycloserine 750 mg, Ethionamide 750 mg, Pyrazinamide 1750 mg, Ethambutol 1000 mg and Pyridoxine 150 mg. He had a history of loss to follow up and treatment failure. Indeed, the Acid Fast Bacillus (AFB) sputum smear was still positive.

During his early treatment of anti MDR-TB drugs, he had normal hearing, liver function, renal function and mental health. He had a mild adverse event, namely nausea and headache, but he managed it by himself. By then he did not have a social problem.

Twenty-eight days after he started the anti-TB treatment, he came to Moewardi Hospital due to agitation, crying and keep moving around to do prays. Then he was hospitalized in Psychiatric ward.

He needed to be assisted in taking care of himself, had sad appearance, was not cooperative, and his eye-contact was present but not adequate. His mood was labile and irritable. Thinking process was not realistic, undergoing loose associations, and guilty ideas were present. The long-term memory was fine while the short-term memory was disrupted. He was diagnosed with acute psychotic schizophrenia, GAF (Global Assesment of Functioning) score was 40-31. The physical condition, especially respiratory symptoms, was not worse. He received Haloperidol 5 mg, Diphenhydramine 10 mg; Cycloserin was stopped and replaced by Para-Amino-Salicylic acid (PAS) 8 grams daily orally. At that time, the other anti-MDR-TB drugs were continued. The psychiatric medication was Risperidone 2 mg every 12 hours orally and continued with psychoeducation to his family and psycho-supportive treatment for him. After 3 days of hospital treatment, he showed improvement by showing anymore symptoms, taking care of himself, being cooperative and normoactive.

Subsequently, he had been in ambulatory treatment in Moewardi Hospital for 4 months. On the fifth month, he was sent back to the Klaten Hospital who referred him at the first place, to continue the treatment. He had family support during his treatment. He finished his treatment on 28th November 2015 or for 24 months treatment and he was labelled as cured.

We continued to follow his clinical progress up until 16 months post-treatment. At that time,we performed quality of life examination with SF36v2 Health survey questionnaire from Quality Metric. He showed a good result, including physical health or mental health. Until today, he has helped the health providers as a motivator for ongoing treatment MDR-TB patients.

Case 2

A 28-year-old woman, affected by pulmonary MDR-TB, started treatment on 5th June 2014, by receiving Kanamycin 750 mg, Levofloxacin 750 mg, Cycloserine 500 mg, Ethionamide 750 mg, Pyrazinamide 1500 mg, Ethambutol 1200 mg and Pyridoxine 100 mg, all of them daily. She also had a history of failure to treatment. At the beginning of the MDR-TB treatment she also showed normal liver function test, renal function, mental status and hearing function. She took the medicine ambulatory regularly.

In the 7th month of treatment, she came with incoherent speech; she was non- cooperative, refused to take medicine, often get daydreaming and locked herself in her room, having thought that someone tried to kill her, refusing to eat and drink. She was diagnosed with acute psychotic GAF score 40-31. Previously she had personal issues because her boyfriend left her to marry someone else. There was no worsening in her clinical condition, as far as the pulmonary TB was concerned.

Cycloserine was stopped and replaced with PAS 8 grams daily; the patient received haloperidol 5 mg, diphenhydramine 10 mg every 12 hours intramuscularly especially when she was agitated. During her calm period, she received haloperidol 5 mg and trihexyphenidyl 2 mg three times daily orally.

After 11 days of treatment in hospital ward, she had improved: there was no more hyperactivity and agitation and she had happy mood with appropriate affect. Therefore, her therapy was switched to oral haloperidol 5 mg and trihexy phenidyl 2 mg three times daily. She had a very good memory and good insight. she had minimal respiratory symptoms, minimal side effects, and there was such an improvement that she was referred to ambulatory treatment.

She was then referred back to the nearest health care facility from her house, which was Primary Healthcare Centers Simo, 10 minutes away from her house.

One month after the referral, she experienced another psychotic disorder. In the health care service there was no management of the psychiatric disorders due to the absence of dedicated health care providers.

Then she ran away to Jakarta,600 kms from her home. Therefore, her presence could not be traced by the health care providers, so she did not finish her treatment.

Discussion

Management of MDR-TB was quite complicated due to the long period of treatment and the numerous drugs that must be used. Those are the cause of the high chance of adverse events, both physical and psychiatric ones, among the MDR-TB patients [7,8]. Some of published research reported incidence of severe depression adverse event rate reaching 6.46% [9], while WHO report stated that psychiatric disorders incidence is 3.6% [5].

This case series describes psychiatric adverse events during management of MDR-TB. Many anti-TB agents are known to be cause of psychiatric adverse events i.e. isoniazid [10], ciprofloxacin [11], ethambutol [10], ethionamide [12] and cycloserine [8,13–16], in this case the culprit drug was cycloserine. Therefore, the administration of cycloserine was stopped. Both patients had history of ethambutol administration withoutpsychiatric symptoms,. The first patient took ethambutol for 11 months and the second took ethambutol for 8 months. Ethionamide was unlikely as cause, since the rare incidence of ethionamide-induced psychiatric disorders. By contrast, the cycloserine-induced psychiatric disorders in MDR-TB is commonly reported, manifesting in many fashions.

Among the ones reported, we can sum up the following ones: visual hallucination and delirium [15], hallucination and *suicidal ideation* [14], paranoid hallucination and grandiose delusion [16], paranoid and delusion [13]. In this case series, the psychiatric symptoms were acute psychosis with severe depression in the first case and acute psychosis with symptoms of depression and paranoid in the second. Both cases have GAF (Global Assesment of Functionary) score 40-31 or some impairment in reality testing or communication. Cycloserine targets the glycine-binding site of N-methyl-D-aspartate (NMDA) receptors in humans. Altogether, Cycloserine seems to have an impact on cognitive functions, mainly those associated with NMDA receptor-dependent mechanisms like long-term potentiation in learning processes [17].

Globally, almost all (69.55%) MDR-TB patients who just started the MDR-TB treatment had a baseline depression. The depression included the fear and guilty feeling that related to infection risk, economy burden, living in chronic disease, the possibility of life threatening condition and the increase of dependency of the others, also the fear of treatment failure for those who had a previous TB treatment [9].

It is not easy to manage depression during the intensive phase in MDR-TB patients. Some factors known to be related to are: younger age (less than 30 years old), female, duration of illness, previous TB treatment, disease extent or co-morbidity [7,9], extra pulmonary TB [7], and monthly income [9].

In our report both patients had similar baseline conditions. They were aged under 30 years old, had history of anti-TB drugs, similar severity of disease, no extra-pulmonary TB , and good social economy status. The difference was only the gender,.

In this report, it seemed that, at the beginning, the female patient could manage her psychiatric side effects. She remained stable for a month after the psychiatric adverse event, but then it relapsed. Women usually have higher level of depression than men. The gender difference is likely due to a complex interaction between biological, psychological and socio-cultural vulnerabilities. Female patients with MDR-TB in developing countries become lonely, underestimated and socially stigmatized [9].

The management of depression is so important so that it may affect the quality of life, which then will affect the compliance of the treatment, resulting in stopping treatment, and increasing in drug resistance. Javaid A, *et al.* (2016) reported that depression is related to treatment outcome [9].

Inadequacy of social support, inappropriate coping mechanism [9] and other psychological factors [18] are some factors related to the unsuccessful management of the psychiatric adverse event. Social support is highly needed in MDR-TB patients especially to manage social stigma, hopelessness, and sense of worthlessness.

Social support is likely to be essential in helping individuals to cope more effectively and to manage some emotional distress related to this problem [19].

Both patients had good social support from their family and friends. The length of stay in hospital due to the psychiatric adverse events lasted less than 2 weeks and they both were discharged in stable condition and always accompanied by their family. Besides social support, another important factor is coping strategies form the patients. Social support may be important in helping individuals but individual willingness is also a determinant in successful management of the psychiatric problems. Coping can be broadly defined as the cognitive and behavioral ways that people manage or adapt to stressful circumstances. Religious faith can be a major coping resource for patients facing serious

illnesses including cancer. Religious people often report the use of positive religious coping, which is characterized by a constructive reliance on religious faith to promote adjustment (e.g., benevolent religious reappraisals and collaborating with God to cope) [20].

Why is religious coping so common among patients with medical and psychiatric illness? Religious beliefs provide a sense of meaning and purpose during difficult life circumstances; they usually promote a positive world view that is optimistic and hopeful; they provide role models in sacred writings that facilitate acceptance of suffering; they give people a sense of indirect control over circumstances, reducing the need for personal control; and they offer a community of support, both human and divine, to help reduce isolation and loneliness. Unlike many other coping resources, religion is available to anyone at any time, regardless of financial, social, physical, or mental circumstances [21].

On both case, the first patient showed his loyalty in worship. He was a Muslim, s, and he always prayed wholeheartedly. After suffering the severe psychiatric adverse event, he had never had another psychiatric disorder until he finished the treatment and declared to be cured. Furthermore, when we performed the quality of life examination, his physical and psychological condition after 16 months were good, and he even became one of the motivator in PMDT for MDR-TB patients. He used coping strategies, religious coping in controlling physical and psychical stressor during the MDR-TB treatment.

The second patient was also a Muslim, but her worship activity was not prominent. She also had a psychological stressor, namely she had been left by her future-husband. She had exacerbation of psychiatric symptoms during her treatment in primary healthcare center which ended up as loss-to-follow-up because she runaway to another city. She failed to develop coping strategies in managing her physical and psychological problems during MDR-TB treatment, resulting in an uncured disease.

Management of MDR-TB in Indonesia at the intensive phase is performed in referral hospital which has comprehensive and specialist treatment provided. Whenever the patients have stable condition and no adverse events, then they can be sent to c ambulatory. Ambulatory treatment can be done in referral hospital and in the nearest health care services to facilitate patients to increase the treatment adherence.

The choice of health care service for ambulatory treatment is based on the capability to manage the adverse events that might occurred during the MDR-TB treatment. However, attention is usually paid on physical adverse events but not on the psychiatric adverse events. Along with the increasing incidence of psychiatric adverse events reports, we need to pay attention more to MDR-TB cases with psychological disorders., Cognitive behavior therapy and social therapy should be offered by the ambulatory care provider.

Psychosocial support is an essential part for the management of adverse effects. Education and encouragement in continuing the treatment are the most important roles played by the DOT (directly observed treatment) provider. Patient support groups are another tool to give psychosocial support to the patients [22]. Professional health care providers with specific skills on identifying MDR-TB patient's mental health status need to be placed on ambulatory health care facility services, therefore patients with psychological disorders can be detected [9]. Nowadays involving medical officer in mental health is highly required, especially for patients who had experienced psychiatric adverse event.

Unfortunately, the healthcare providers with such skills are lacking, being total absent in some remote places. It is a great challenge saving MDR-TB patients from suffering the psychiatric adverse events during their ambulatory treatment in their home community [23,24]. It is important to increase healthcare personnel trained to detect the psychiatric adverse events in MDR-TB patients.

Conclusion

Psychiatric adverse events during MDR-TB treatment are increasing lately. The probable cause of this adverse event in this case series is cycloserine. Generally, when in the intensive phase of MDR-TB treatment, patients usually suffer from depression because they are worried for their life and fear recurrent treatment failure. Social support is highly required in managing psychological problems in this setting, both from their family and friends. t. Implementation of effectively coping strategies is required such as religious coping in managing the psychological problems. The availability of trained and skilled healthcare personnel to detect the psychiatric adverse event during ambulatory treatment is important in preventing and treating MDR-TB patient who has risk in undergoing psychiatric disorders.

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