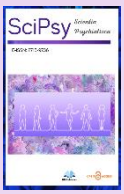

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Depression in Tuberculosis Patient: A literature Review

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A B S T R A C T

Tuberculosis is one of the infectious diseases with the highest burden with the highest morbidity and mortality in the world. Tuberculosis is divided into two groups: latent tuberculosis and active tuberculosis. The diagnosis of tuberculosis can be established through anamnesis and investigations. Tuberculosis is often associated with levels of depression, the high incidence of depression in tuberculosis patients is caused by various factors including biological factors of the immune response system (IFN-g agents, TNF, IDO NALP3), social factors and behavioral factors. Management of anti-depressant therapy that is recommended as the first line is the SSRI group. Furthermore, patients with drug withdrawal or treatment failure, high risk of drug resistance, bad stigma about their disease will increase the risk of depression.

1. Introduction

Tuberculosis is one of the highest burdens of disease worldwide with poor morbidity and mortality rates, especially in low-wage developing countries.[1] Mycobacterium is a bacterial organism that causes tuberculosis, rod-shaped and acid-fast. spread of infection through the air from human to human, affecting the lungs and other parts of the body.[2] In 2019, World Health Organization report the estimated incidence was 10.0 million million people fell ill with tuberculosis, 1.5 million people died of tuberculosis and 484,000 people fell ill with drug-resistant tuberculosis in 2018.[3] Efforts to eradicate TB saved the lives of 58 million people worldwide between 2000 and 2018.The greatest illness burdens were recorded in South-East Asia (44%) – with India accounting for 27% of all cases – and Africa (24 percent).[4] The treatment is provided through the Directly Observed Treatment Shortcourse (DOTS)and cure rates have been reported to be 80%. The DOTS program as one of the most effective health interventions refers to an antibiotic treatment approach in which health workers observe patients taking medication them every day or three times a week.[5] The most effective health intervention for the treatment of tuberculosis is the implementation of the DOTS (Directly Observed Treatment Shortcourse) strategy. As one of the efforts to tackle tuberculosis, medical personnel will conduct periodic observations of patients, monitor drug consumption compliance. The level of drug adherence is influenced by various factors including poor health services, low socioeconomic level, mental health disorders, depression, and drug use, which adversely

affect patient treatment. Withdrawal or failure of therapy can increase the incidence of drug resistance by being associated with the onset of depression.[6]

Depression is one of the common mental health problems in tuberculosis patients, characterized by mood swings, feelings of constant stress, feeling inferior, unappreciated, always feeling wrong, lack of interest, easily tired, unfocused, feelings like wanting to hurt yourself. alone. Depression results in varying degrees of social and occupational dysfunction.[7] Tuberculosis and depression often coexist in individuals. They share the same risk factors, and high comorbidity ranged from 10% to 52%.[8-9] People with depression have increased pro-inflammatory cytokines that lead to reduced activation of the humoral and cellular immune systems that contribute to the development of tuberculosis.[10] Likewise, infection due to tuberculosis can cause chronic inflammation, releasing pro-inflammatory cytokines that stimulate enzymes that function in the central nervous system and also some anti-TB drugs may play a role in mental health problems such as depression.[9] When depression is comorbid with tuberculosis, it will lead to poor quality of life, lack of adherence to anti-TB drugs, progression to MDR TB and ultimately to death from the disease.[10]

Risk factor of tuberculosis

There are several risk factors that cause tuberculosis infection, the main population factors for infection in developing countries are below average socioeconomic conditions, unequal health care and difficulty in accessing care, population density, high incidence of HIV, smoking is not in the area and alcohol free.[11-12] Tuberculosis is also associated with other diseases that make the development of infection easier, especially in disease conditions that suppress the human immune system so that it is susceptible to tuberculosis infection, other disease factors related to tuberculosis are diabetes mellitus, lymphoma, end-stage renal function disorders, post organ transplantation. and immunosuppressive conditions, HIV.[11-12] Malnutrition is one of the important risk factors that can increase the incidence of tuberculosis through an impaired immune response process, but basically there is a two-way relationship between the two because tuberculosis can lead to malnutrition due to changes in metabolic processes, drug interactions, so that patients experience decreased appetite. The social and economic status of a person is also the most important driving factor for tuberculosis, especially in developing countries.[13] People with below-average socioeconomic status have a higher risk of infection because the place to live is not suitable for the large number of family members, inadequate ventilation circulation, limited facilities for shared household appliances and difficult access to health.[13]

Symptoms and Signs of Tuberculosis

In latent tuberculosis, the pathogenic bacteria are inactive or do not replicate (dormant) in the human body. people who carry out examinations to establish a diagnosis of disease through immunological tests and chest X-ray examinations with positive results but in patients without symptoms and showing no signs of active tuberculosis, therefore the patient cannot infect others.[14] However, latent tuberculosis can turn into tuberculosis is active in the future, especially in conditions of immune disorders so that it can infect other people. It was reported that the first 18 months after infection with Mycobacterium tuberculosis can develop into active as much as 5% and the rest can develop for the rest of life.[15]

Active pulmonary tuberculosis can cause clinical symptoms of infection and can transmit to other people, the typical symptoms of tuberculosis are low-grade fever at the onset of symptoms, productive cough with phlegm, coughing up blood (hemoptysis), night sweats and symptoms of toxemia such as unusual tiredness, irritability. malaise, weight loss, and headache.[14-15] Should be considered in patients who have a persistent persistent cough that lasts more than 3 weeks, the likelihood of developing tuberculosis infection increases.[15] Further symptoms such as shortness of breath are associated with the development of widespread infection in parenchyma,

while at the end of the course of the disease caused by tracheobronchial obstruction.[16] Partialy of the patients also experience further symptoms of chest pain which is usually localized and pleuritic.[16] tuberculosis can develop slowly in adults who do not have a history of immunocompromise. However, in people with a history of impaired immune function and in children, the development of infection is more rapid and the risk of developing fulminant tuberculosis increases rapidly. 1-2 Meanwhile, extrapulmonary tuberculosis that distinguishes symptoms from pulmonary tuberculosis usually involves more than one organ system that influences each other and has an increasing incidence in patients with immune system disorders.[16]

Pathogenesis of tuberculosis

Mycobacteroium tuberculosis which consists of several mycobacteria related to tuberculosis, in the form of non-motile and aerobic bacilli, will enter through exposure to air, droplets enter the mouth and nasal cavity then into the upper respiratory tract, enter the bronchi, and the final process is at the alveolar stage in the lungs.[17-18] The process of infection developing in the lungs will form a "classical mycobacterium tuberculosis" complex. the quantity of bacteria that infect tuberculosis is very little less than 10 bacteria alone can cause the body to become infected. After bacteria enter the alveoli, they will be phagocytosed by macrophages in the alveoli, causing the process of inhibition and destruction of tubercle bacilli.[18] The granulomatous inflammatory process in the alveoli in the lungs through a response by macrophage receptors, epithelial cells and dendritic cells interacts with mycobacterial bacteria to produce cytokine and chemokine agents to form granulomas through the patient's immune system.[18] The initial interaction of mycobacterial organisms with the patient's host will cause clinical manifestations of primary tuberculosis, there is a 'Ghon focus' which is located in the middle of the curve and is fixed, most infected with 'Ghon focus' is primary tuberculosis entering the latency phase. The tubercle bacillus is controlled, then it will form a condition in which latent tuberculosis infection (LTBI).[18-19] In this condition the patient does not show symptoms and is not infectious.4 However, if the immune system cannot be controlled, the tubercle bacilli will replicate rapidly, especially in special conditions such as immune system disorders.[19] The process of developing tuberculosis disease can be very fast after being post-infected in the latent tuberculosis phase, it can also reactivation for many years throughout the life span. In the condition of patients with active tuberculosis, it can be easily transmitted to other people.[20]

Diagnosis of tuberculosis

Establishment of the diagnosis of pulmonary tuberculosis is assessed from a history of previous disease, clinically significant symptoms, microbiological examination of tuberculosis bacteria and chest X-ray examination. However, the main standard of examination is microbiological culture but it takes a long time, the results are around 8 to 10 weeks.[22] Another immunological examination that can be used is the examination of the release of gamma interferon assay (IGRA) which is used to detect patients who have had previous tuberculosis infection but cannot detect active infection. Tuberculin skin test (TST) is commonly used in children.[23] An examination that is often used in hospitals and recently introduced is the polymerase chain reaction (PCR) examination, how it works by recognizing nucleic acid sequences and being able to recognize drug resistance, this test can improve the diagnosis of tuberculosis.[24] The accuracy of the sensitivity of this PCR test varies as much as 67% in patients with negative sputum and 89% when used at the beginning of the test to establish tuberculosis.[25] Supportive examinations are available in all hospitals at an inexpensive cost, chest X-ray examination is important in establishing a diagnosis, screening for disease, and assessing response to anti-tuberculosis therapy. However, CT scan imaging is superior for assessing the characteristics of localization of spread, assessing extrapulmonary or disseminated tuberculosis and also

better for assessing mediastinal lymphadenopathy 91%.[24]

Role of depression in patient tuberculosis

In general, there is an association of tuberculosis with the incidence of depression, but it is difficult to assess which symptoms of the disease appear first. The high level of vulnerability of tuberculosis sufferers often has an impact on depression, one of which is the effect of depression on the immune system which is a systemic source of acute and chronic stress, which affects various functions including brain, neuroendocrine and behavior.[25] Symptoms of depression will be induced through a conscious increase in cytokines resulting from the activation of the inflammatory response in tuberculosis.[25-26] The inflammatory response is often referred to as biological factors and other factors that influence the susceptibility of the synergistic relationship between the two groups are explained synergistically by social and behavioral factors.[26]

Response inflammatoty system mediating the depression and tuberculosis

Biological factors of susceptibility between tuberculosis and depression are explained through the inflammatory response system that plays a role in the pathophysiology of infectious diseases.[27] Symptoms of depression will be induced by increased levels of cytokines, cytokines are inflammatory agents between the IFN-g and TNF-a lines that function to regulate the enzyme indolamin 2,3 dioxygenase (IDO) to activate kynurenine, the function of the kynurenine enzyme makes the synthesis of serotonin levels in the central system decrease. The product of kynurenine metabolism also acts as a neuroactive which also plays a role in tryptophan levels associated with depressive symptoms. Indolamin enzymes have an important role in people with depression and inflammatory diseases.[28] Another inflammatory response that functions in the inflammasome protein 3 (NALP3) complex which is activated by Mycobacterium tuberculosis, it contains LRR, PYD and NACHT which play a role in 'caspase' activation, in the first caspase a cytosolic cleavage process occurs and the release of IL-1β. Mycobacterial organisms were associated with the inflammasome protein 3 process in the initial control.[29] The release of IL-1β and TNF-α is also related to the uptake of neutrophil agents and fibroblast activation, the inflammatory process and activation are related to the severity of damage to the lung cavity in tuberculosis patients.[30] In depressed patients it will produce excessive IL-1β which has a negative impact on the inflammatory response.[30]

Social and behaviour factor of tuberculosis and depression

The risk factor that causes the high incidence of tuberculosis with depression is the level of poverty, a condition where a person has difficulty meeting the necessities of life. Poor air circulation and overcrowding encourage the transmission of tuberculosis to be higher.[31-32] A below-average standard of living makes people more susceptible to stress including being vulnerable to violence, feeling socially isolated, and drug abuse, which increases the risk of developing depressive symptoms.[33] Anxiety about diagnosis and prognosis, as well as possible isolation from social, stigmatized tuberculosis can increase the risk of depression. Depression can amplify and imitate tuberculosis auxiliary symptoms, such as low appetite, weight loss, and easy fatigability. People with depression are more likely to engage in negative coping behaviors such as drug addiction, which adds to poverty, hunger, and a weakened immune system. Furthermore, sad people are more prone to engage in poor self-care, eat poorly, and struggle to stick to complicated treatment regimens. Due to reactivation of latent TB, it increases the prevalence of TB in these individuals, as well as delays in health care and poor drug adherence rates increase morbidity and mortality.[33]

The impact of anti-tuberculosis drugs with antidepressant

The most recommended antidepressant treatment is SSRI (selective serotonin reuptake inhibitor), which is the first-line treatment option and is the most preferred by clinicians for the treatment of patients with depressive disorders. Another treatment option is MAOIs (Monoamine oxidase inhibitors) which have mild side effects.[34] However, in comorbid tuberculosis, there is a drug interaction between SSRIs and isoniazid tuberculosis therapy.[33] Isoniazid functions to inhibit the action of monoamine oxidase in blood plasma.[34] Other anti-depressants are TCAs (tricyclics), the combination of TCA and SSRI drugs is not recommended to be given together with drugs that inhibit the action of monoamine oxidase because it causes serotonin induced syndrome. However, there is no further evidence that is significant between the potential drug interactions of isoniazid and anti-depressants that are mutually detrimental to each other. On the other hand, at the molecular level, there is a significant association between isoniazid and SSRIs through the mechanisms and metabolism described previously. Metabolism of drugs fluvoxamine, paroxetine, sertraline, isoniazid, citalopram, and fluoxetine on average mostly metabolized in the liver by cytochrome P450 enzymes. The pharmacokinetics of several drugs vary, it is explained that SSRI drugs have better drug interactions with anti-TB drugs than other antidepressants. One of the anti-TB drugs of choice is isoniazid and rifampicin.[33-34]

2. Conclusion

The high incidence of depression in tuberculosis patients needs further attention for better treatment and improvement of the patient's quality of life. This review confirms that in general, there is an association of depressive symptoms in tuberculosis patients. Patients with tuberculosis have a high risk of depression. What needs to be considered in the future is that the problem of drug interactions between antidepressants and antituberculosis should be investigated further.

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