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Analysis of Liver Function on Leprosy Patient with Multidrug Therapy in Haji Adam Malik General Hospital Medan from January until December 2017

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Abstract

Leprosy is a chronic progressive granulomatous disease that caused by *Mycobacterium leprae*, an intracellular obligate bacteria. Leprosy can be treated using multidrug therapy (MDT) that can be associated with hepatotoxicity as their side effects. We included 14 patients that were all diagnosed with multibacillary leprosy, but with four drops out persons. Liver function evaluations before MDT were in the normal range. After 1st, 2nd, and 3rd months of MDT, liver function test in research subjects also in the normal range even though there is variation in this value. There is a risk of hepatotoxicity of MDT; therefore, liver function test should be done periodically for early detection of any liver dysfunction.

Introduction

Leprosy is a chronic progressive granulomatous disease that caused by *Mycobacterium leprae*, an intracellular obligate bacteria [1]. Leprosy can affect peripheral nerve and skin and other organs except central nervous system [1], [2], [3]. This disease is endemic in many tropical and subtropical countries, including Brazil, India, and Indonesia. These countries contribute to 82% of new leprosy cases globally [4], [5], [6].

In 2014, there are 17.025 new leprosy cases reported from Indonesia and 83.5% of these cases were classified as multibacillary (MB) leprosy, whereas according to gender, 62.6% of leprosy patients were male and 37.4% were female [3]. According to the prevention and control of tropical disease in Indonesia on 2017, there were 15.910 new leprosy cases in Indonesia, and 158 of these cases can be found in North Sumatera Province. Data of new leprosy patients according to the medical record of Haji Adam Malik General Hospital Medan in 2015, are 16 cases, 2016, with 19 cases and 2017 with 14 cases.

According to the WHO, leprosy can be classified into paucibacillary (PB) and MB type [7]. Leprosy can be treated using multidrug therapy (MDT), a combination of two or more anti-leprosy drug such as rifampicin, dapsone, and clofazimine. Rifampicin and dapsone are the most important medication that given to both PB and MB leprosy [8]. Metabolism of rifampicin and dapsone are both occur in the liver, include hydroxylation and oxidation by cytochrome P450 enzyme [9], [10]. However, research by Dhavalshankh *et al*. describe that liver function dysfunction can be found in leprosy patient even before MDT [11].

Swathi in India reported that there were significant differences in total protein serum between the case and control group [1]. The result of a study by Bjornsso in Sweden found that 22.9% subjects showed an increase of bilirubin more than 2 times of normal value and more than 3 times increase of alanine transaminase (ALT) [12]. Research by Tsankov and Kamashev in Bulgaria concluded that hepatotoxicity of the earliest complication can be found from rifampicin [13].

There are several parameters that can be used to detect liver dysfunction such as total bilirubin serum level, ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, albumin, and globulin [1], [8], [14]. Evaluation of liver function is carried

out every 4 weeks for 3 months of medication [1], [15], [16]. If there is an increase of more than 2–3 times the normal limit, the medication can be stopped temporarily and the patient should be monitored [15].

Until now, research on leprosy medication and its side effect in Indonesia, especially in North Sumatera, is still very limited, while MDT is still part of the Ministry of Health Republic of Indonesia Program to manage and eradicate leprosy. Therefore, we wanted to analyze the liver function test before and after MDT in 3 months on leprosy patients in Haji Adam Malik General Hospital Medan.

Methods

This is descriptive research with case series on all leprosy patients that came to Leprosy Division in Dermatology and Venereology Department of Haji Adam Malik General Hospital Medan from January to December 2017. Liver function tests were done in the Clinical Pathology Laboratory of Haji Adam Malik General Hospital Medan. Inclusion criteria are include new leprosy patient that diagnosed with PB and MB leprosy that has not been treated with MDT; agree to be included in this research by signing the informed consent; age between 18 and 60 years old. Exclusion criteria include pregnancy; a patient that consumes systemic medication of other diseases or other hepatotoxic medication; a patient that stopped taking MDT; chronic alcohol consumption; and had a history of jaundice and other liver diseases.

Research subjects who had signed the informed consent form were had their blood taken for liver function test, which include total bilirubin serum, ALT, AST, ALP, total protein, albumin, and globulin before MDT. These subjects were then had their blood taken again for another liver function test after 1, 2, and 3 months of MDT. The data were collected and analyzed using statistical software. A descriptive analysis was carried out to determine the mean and standard deviation value of variables that were studied. This research was carried out after obtained ethical clearance from the Research Ethics Committee of Faculty of Medicine, Universitas Sumatera Utara.

Results

There were 14 patients that were included in this research and all of them were diagnosed as MB leprosy, but there were four drops out persons. The majority of these patients were male (70%) and there were six subjects that age more than 30 years old. Blood examination for liver function before MDT showed a normal mean value of total bilirubin, ALP, ALT, AST, total protein, and albumin, whereas mean value of globulin was higher than its normal range.

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Table 1: Sex and age characteristics of leprosy patients

Characteristics	Leprosy patients	
	n	(%)
Gender		
Male	7	70.0
Female	3	30.0
Age		
≤20	3	30.0
21–30	3	30.0
3–40	2	20.0
≥40	2	20.0

Highest bilirubin level was found after 1 month of MDT with 0.61 mg/dl (SD = 0.28 mg/dl). Lowest bilirubin level was found before MDT with 0.43 mg/dl (SD = 0.22 mg/dl). The highest level of ALT was found after 1 month of MDT with 33 U/L (SD = 32.52 U/L), while the lowest level was seen after 3 months of MDT with 17.4 U/L (SD = 6.7 U/L). The highest level of AST was seen after 1 month of MDT with 30.5 U/L (SD = 21.96 U/L) and the lowest level was seen after 3 months with 22.2 U/L (SD=4.47 U/L).

Table 2: Liver function test in leprosy patient with MDT medication

Liver function test	Before MDT	After 1 month	After 2 months	After 3 months	
Total bilirubin	0.43±0.22	0.81±0.54	0.61±0.28	0.63±0.24	mg/dl
ALT	22.7±14.61	33±32.52	24.6±19.78	17.4±6.7	U/L
AST	25.1±12.27	30.5±21.96	22.4±8.03	22.2±4.47	U/L
ALP	78±28.04	95.7±56.47	68.6±21.37	67.4±22.33	U/L
Total protein	7.89±1.29	7.67±1.31	7.49±1.22	7.72±1.29	g/dL
Albumin	3.66±0.75	3.62±0.59	3.68±0.79	3.89±0.64	g/dL
Globulin	4.23±1.79	4.05±1.63	3.81±1.84	3.84±1.67	g/dL

MDT: Multidrug therapy, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase.

The highest level of ALP was seen after 1 month of MDT with 95.7 U/L (SD = 56.47 U/L) and the lowest was found after 3 months of MDT with 67.4 U/L (SD = 22.33 U/L). Total protein was the highest before MDT with 7.89 g/dl (SD = 1.29 g/dl), but the lowest was seen after 2 months of medication with 7.49 g/dl (SD = 1.22 g/dl).

Albumin was highest at 3 months after medication with 3.89 g/dl (SD = 0.64 g/dl) and the lowest was found after 1 month of MDT with 3.62 g/dl (SD = 0.59 g/dl). The highest level of globulin was seen before medication with 4.23 g/dl (SD = 1.79 g/dl), while the lowest level of globulin was found after 3 months of MDT with 3.81 g/dl (SD = 1.84 g/dl).

Discussion

This research involved 14 research patients with the majority of male and age <30 years old. Data from Indonesia also showed that leprosy is often seen in male than female [3]. According to a study by Moet *et al.*, age and gender are risk factors of leprosy. This probably happens because male has more interaction

with other people due to work, therefore, more prone to infection than female [17], [18]. Besides, we did not identify any side effects of MDT in all subjects.

Liver function evaluations before MDT were in the normal range. An increase in transaminase serum level usually seen in lepromatous leprosy type patients [19], whereas in patients with borderline and tuberculoid type usually show normal ALT, AST, and ALP level [20]. Several research showed an increase of bilirubin serum in lepromatous type. Dhavalshankh *et al*. found that bilirubin level did not increase significantly in multibacillary and paucibacillary type leprosy. However, there is an increase in mean globulin value compared to its normal range. This research also showed that patients with multibacillary leprosy had a significant decrease of albumin level, but it is not significant in globulin level [11]. Most globulin protein is produced by the liver; however, globulin in the form of immunoglobulins is produced by plasma cells [21]. This can affect globulin levels from the research subject.

Medication using MDT in leprosy patients can cause abnormal liver function, which usually caused by Rifampicin and Dapsone [22]. Research by Deps *et al*. showed abnormality of liver function that caused by Dapsone can be seen in 20 of 85 patients, whereas rifampicin consumption caused abnormal liver function in 10 out of 24 research subjects [21]. Other reports showed that rifampicin is causing hepatotoxicity in <1% patients [23].

In research subjects, laboratory examination in the 1st, 2nd, and 3rd months after MDT showed normal liver function even though there is variation in this value. The majority of patients can tolerate the side effects of rifampicin and dapsone with appropriate dosage [13], [24], [25]. However, evaluation of liver function still needs to be done to identify an abnormal liver function as early as possible [23].

Conclusion

The current research showed a normal liver function test before MDT, which includes total bilirubin serum, ALT, AST, ALP, total protein, albumin, and globulin. Moreover, there is no difference between liver function test after 1 month, 2 months, and 3 months of MDT in leprosy patients in Haji Adam Malik General Hospital Medan. However, there is a risk of hepatotoxicity of MDT; therefore, we advised doing liver function tests periodically for early detection of any liver dysfunction.

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