REVIEW

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The role of anti-phenolic glycolipid-1 serological test in leprosy

Ni Luh Putu Ratih Vibriyanti Karna, Anak Agung Indah Jayanthi*, Desak Nyoman Trisepti Utami

Dermatology and Venereology Department, Medical Faculty of Universitas Udayana/ Sanglah General Hospital Denpasar, Bali- Indonesia;

*Corresponding author:
Anak Agung Indah Jayanthi;
Dermatology and Venereology Department, Faculty of Medicine Universitas Udayana/ Sanglah General Hospital Denpasar, Bali- Indonesia;
agungindah87@gmail.com

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ABSTRACT

The number of new leprosy cases in the world is surprisingly high, Indonesia is still at the third rank in the term of new leprosy cases over the world. Leprosy control strategies can be successful if early diagnosis and appropriate therapy are carried out. Currently, several serological tests have been developed which can help detecting subclinical leprosy, making the diagnosis, and monitoring therapy. One such serological tests is the anti-Phenolic Glycolipid-1 (PGL-1) serological test. The antibody response to PGl-1 is mainly IgM, the amount of this antibody is correlated to the number of bacteria; so, the titer is higher in lepromatous type compared with tuberculoid type, this causes serological tests still have limitation in diagnosing leprosy, especially in paucibacillary type leprosy.

Keywords: leprosy, PGL-1, serological test.
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INTRODUCTION

Leprosy in developing countries, especially in leprosy endemic countries, is still a health problem today.[1] The number of new leprosy cases in the world is still high, around 208,641 cases in 2018. The number of leprosy cases in the Southeast Asia Region is 148,495 cases which is the highest leprosy case in the world. The number of new leprosy cases in Indonesia is 17,017 cases, and reaches the third rank in the world after India and Brazil.[2] The number of new cases which is still high can be caused by the number of individuals with subclinical leprosy infection that remains unidentified, and if untreated, it is possible to manifest as leprosy at a later time.[3,4] Diagnosis and classification of leprosy mostly still refers to clinical assessment of the cardinal signs of leprosy, microscopic detection of acid-fast bacilli (AFB) on slit skin smear or biopsy. None of these diagnostic approaches has been able to detect *M. leprae* infection in subclinical leprosy.[5,6]

The key components in a leprosy control strategy are early diagnosis and appropriate therapy. Currently, several serological tests have been developed to help detect subclinical leprosy and establish an early diagnosis. One of the serological tests that can be done is checking for phenolic glycolipid-1 (PGL-1) antibody.[5,6] *Phenolic glycolipid-1* is one of the specific antigens in capsule and cell wall of *M. leprae*.[7,8] The PGl-1 antibody is mainly IgM, the amount of this antibody is correlated to the number of bacteria, so the titer is higher in lepromatous type compared with tuberculoid type.[6,7] This literature review will discuss the *Phenolic glycolipid-1* serological test in people with leprosy, so that it is expected to improve understanding of the role of the anti-PGL-1 serological test in detecting subclinical leprosy, diagnosing leprosy, monitoring response to multi-drug therapy (MDT).

PHENOLIC GLYCOLIPID-1 AS A SPECIFIC ANTIGEN OF *MYCOBACTERIUM LEPRAE*

An antigen is any material that can be identified specifically by lymphocytes and antibodies. Several studies over the past three decades have attempted to develop serodiagnostic assays using specific *M. leprae* antigen and specific antibody epitopes.[6] The ultrastructural details of *M. leprae* are the capsule, cell wall, cell membrane, and cytoplasm, which can be seen using an electron microscope. *M. lepra* capsules contain bacterial lipids which are found in large numbers in infected tissue. The two main bacterial lipids are Phthiocerol dimycocerosate which has a protective function, and PGL-1 which is the dominant lipid in the cell wall, which gives immunological specificity to *M. leprae*.[8,9] Brennan and Barrow found a specific lipid in the cell wall of *M. leprae* which is known as PGL-1.[8]

Lateron, trischarride[3,6-di-O-methyl-β-d-glucopyranosyl-(1→4)-2,3-di-O-methyl-α-l-rhamnopyran(1→2)3-O-methyl-α-l-rhamnopyranose] and the disaccharide components of PGL-1 were found to be the components which react specifically with IgM antibodies in patients'sera.[6] Later, identification of specific B-cell epitopes of PGL-1, the sugar molecules, natural disaccharide (ND)/ natural trisaccharide (NT) led to synthesis of these sugars and were used conjugated with bovine serum albumin (BSA) as ND-O-BSA/NT-O-BSA in ELISA for diagnosis of leprosy. These glycoconjugates were to have higher specificity than the copolymers of PGL-1 and used in standardization of ELISA for diagnosis of leprosy.[6,8] PGL-1 antibody examination can use several techniques, namely Enzyme-linked immunosorbent assay

(ELISA), Mycobacterium leprae dipstick (ML dipstick), and Mycobacterium leprae lateral flow assay (ML Flow) test.[6]

ANTI PHENOLIC GLYCOLIPID-1 SEROLOGICAL TEST IN SUBCLINICAL LEPROSY DETECTION

The spectrum of clinical manifestations in leprosy is related to the immunological status of the host. Paucibacillary (PB) type leprosy, with few M. leprae seen in tissues but strong cell-mediated response whereas multibacillary (MB) type leprosy with large numbers of M. leprae with strong but ineffective humoral response. Between paucibacillary and clinical extremes of multibacillary leprosy there is a borderline type. However, individuals can become infected with *M.leprae* without developing clinical signs of disease.This subtle situation is called subclinical leprosy.[10] In subclinical leprosy patients, the specific antibody against *M. leprae* was found quite high.[11] When compared with the general population, the risk of contracting leprosy in household contacts is 5-10 times greater.[1] Several studies have shown that people with subclinical leprosy can be a source of transmission, but this is still being debated.[12]

Antibody titers appear to be more closely associated to the *M leprae* infection rate in the wider community, although antibody detection may indicate current or past M. leprae infection regardless of clinical signs. This is because the distribution of seropositivity in groups of household contacts or leprosy cases has not been proven to be higher than non-contacts in highly endemic areas; however, significant differences exist between contacts and noncontacts in areas of lower endemicity.[13]

A study conducted by Dias et al. with a total sample 69 who were 4–15 years of age living in the neighborhood [peridomiciliary (PD) contacts] or inside an index case's home [household contacts (HH)] were included in the study. The PD contacts were considered to be those living up to five houses on either side of the index case's home. The index cases diagnosed between 2011 and 2015 were classified as either are multibacillary or paucibacillary. This study concluded there was a positive correlation between anti-PGL-1 IgM levels among MB contacts and among PB contacts, and found a stronger correlation in MB contacts.[13]

Wardana et al. (2016) conducted a cross-sectional study which measures anti-PGL-1 IgM using lateral flow test. The sample in this study were 73 contacts and 28 leprosy patients. Lateral flow examination was found from 73 contact persons, 11 people were positive (15.06%) and almost all positive results (27; 96.42%) for patients with only 1 patient showing negative results. The conclusion of this study is that 15.06% of contact persons suffer from subclinical leprosy and the lateral flow test is effective for detecting *M. leprae* infection.[1]

A meta-analysis study conducted by Penna et al. (2016) concluded that leprosy contact persons are more likely to suffer from leprosy in the future, but not everyone infected with *M. leprae* will manifest as a clinical disease of leprosy. The risk of developing leprosy is roughly 3 times higher in those who are positive to anti PGL1 than in those who are negative. The sensibility of the PGL-1 test as a predictor of clinical leprosy development was below 50% for all studies.[14]

ANTI PHENOLIC GLYCOLIPID-1 SEROLOGICAL TEST IN LEPROSY DIAGNOSIS

The diagnosis of leprosy is based on the cardinal signs of leprosy, According to WHO recommendations, patients are considered paucibacillary (PB) are patients who have a number of lesions up to 5 lesions and multibacillary (MB) patients are those who have a number of lesions more than 6 lesions. About 70% of people with leprosy can be diagnosed through the presence of hypoanesthetic skin lesions. However, 30% of leprosy patients, including the MB type, do not show these signs.[13] Serological tests have an important role in helping to establish the diagnosis of leprosy even though they have limited capacity. In endemic areas where other dermatological diseases are also present, serological tests can be used to exclude leprosy as a possible cause of skin lesions.[15]

First step for leprosy diagnosis is the Clinical evaluation, which is generally sufficient for most cases; however, may not be effective in recognizing early signs of the disease if done by untrained health practitioners. A detailed dermatological and neurological examination can be time consuming. World Health Organization (WHO) has already included microscopic examination of a slit-skin smear in the case definition; nevertheless, almost 70% of all leprosy patients are smear negative. Anti-PGL-1 IgM antibody examination has a role in establishing the diagnosis of leprosy. Based on a systematic review and meta analysis of 78 studies, most of those evaluating the detection of IgM antibodies against PGL-1 using ELISA. Sensitivity of the 39 studies evaluating ELISA was 63.8% and specificity 91.0%. The lateral flow test (nine studies) and the agglutination test (five studies) had a slightly higher sensitivity and a slightly lower specificity.[16]

A study conducted by Leturiondo et al. (2019) used ML flow test (PGL-1 and NDO-LID) to diagnose leprosy. This study found that the ML flow PGL-1 in PB type leprosy had a sensitivity of 32%, specificity of 75.9%, positive predictive value (PPV) was 11.1%, and negative predictive value (NPV) was 92.2%. In patients with MB type leprosy, the ML flow PGL-1 test sensitivity was 81.0%, specificity was 75.9%, PPV was 43.4%, and NPV was 94.6%. Serological test is an effective tool in the diagnosis of MB leprosy but this test is not efficient for the diagnosis of PB leprosy.[15]

CORRELATION BETWEEN ANTI PHENOLIC GLYCOLIPID-1 ANTIBODY AND MULTIDRUG THERAPY

A reduction in antibody levels after MDT, especially for PGL-1, has been reported in several studies. Most of the MB type leprosy had a high bacterial index at diagnosis, although during MDT therapy there was a decrease in antibody levels, most patients remained low seropositive after completing 2 years of treatment.[17]

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leprosy treatment with MDT has long duration of 6 months for paucibacillary (PB) and 12 months for multibacillary (MB) cases. In addition, treatment is complicated by episodes of erythema nodosum leprosum (ENL) and [reversal reactions (RRs). It is necessary to monitor therapy to assess the success of therapy, in addition to assess the side effects that can occur.[18]

ANTI PHENOLIC GLYCOLIPID-1 SEROLOGICAL TEST IN LEPROSY REACTION AND RELAPSE IN LEPROSY

A high bacterial index has been associated with high antibody levels and the development of leprosy reactions and neuritis. Erythema nodosum leprosum (ENL) is a type III hypersensitivity reaction based on the Coombs and Gell classification or the Arthus phenomenon, which involves an antigen-antibody and complement reaction which then causes inflammation of the skin, nerves and other organs. At the location of the ENL lesion, IgG, IgM, and complement (C3) and *M.leprae* antigen were identified.[19]

High levels of anti-PGL-1 antibodies at diagnosis or after treatment are associated with a higher risk of developing leprosy reactions, particularly ENL. Patients with high concentrations of anti-PGL-1 IgM antibody at the start of treatment have a higher risk of developing a reaction, so identifying patients for early monitoring and treatment can reduce nerve damage and disability. In the post-MDT reactions, patients with positive PGL-1 serology when completing MDT were 10.4 times more likely to experience a reaction compared to serologically negative patients.[19]

A longitudinal study conducted by Devides et al. which includes newly diagnosed leprosy patients who presented with or without a leprosy reaction within the diagnosis period between 2009 and 2010. Patients without reactions were monitored during and after MDT for the onset of reaction episodes for five years starting from the time the diagnosis of leprosy was established. During five years of follow-up, among the 151 patients enrolled in the study with no reaction at the time of initial diagnosis, 29 exhibited reactional episodes during and/or after MDT: 5 (3%) RR/ENL, 3 (2%) ENL, 21 (14%) RR, and 3(2%) ENL. In this study, it was found that 29 study subjects who experienced leprosy reactions showed high serological levels for anti-PGL-1 IgM antibody compared to the serological results of 122 subjects who did not experience any reactions. Patients with ENL showed significantly higher serologic titers at preliminary diagnosis. The results obtained in this study indicate that serological testing contributes to the early diagnosis of ENL reactions.[20]

Patients with lepromatous (LL) leprosy showed a significant increase in IgM PGL-1 antibody titers during the relapse period. Tuberculoid leprosy (TT) / borderline tuberculoid (BT) cases that relapse as a borderline lepromatous (BL) / lepromatous leprosy (LL) type can also be detected by measuring anti-PGL-1 antibodies.[1,20]

CONCLUSION

Phenolic glycolipid-1 (PGL-1) is the specific antigen of *M. leprae.* The number of *M. leprae* has a positive correlation with anti-PGL-1 IgM antibody titers, so that the PGL-1 IgM antibody test plays an important role in detecting subclinical leprosy and the occurrence of relapse in leprosy, but the role of serological tests in diagnosing leprosy still has a limited capacity, especially in PB type leprosy due to the small number of *M leprae* bacteria. In administering MDT, serological tests can help the process of monitoring the success of MDT, shown by decreasing the PGL-1 IgM antibody titer in accordance with the decrease in the number of *M leprae*. In the ENL leprosy reaction, a type III hypersensitivity reaction occurs which involves an antigen-antibody and complement reaction, resulting in an increase in IgM anti PGL-1 titer.

CONFLICTS OF INTERESTS

The authors declare that they have no relevant conflicts of interest.

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AUTHORS CONTRIBUTIONS

Author NLPVK, AAIJ, and DNTU contributing from the idea to construct the main topic to manuscript preparation and publication.

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