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Relationship between Leprosy Suspicion Questionnaire with IgM anti-PGL-1 antibody levels in household contacts of leprosy

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ABSTRACT

Introduction: Leprosy is a chronic granulomatous disease affecting mainly the skin and peripheral nerves caused by the obligate intracellular pathogen *Mycobacterium leprae.* This study aimed to determine the relationship between Leprosy Suspicion Questionnaire (LSQ) and anti-PGL-1 IgM antibody levels in household contacts of leprosy patients.
Methods: This research was an observational analytical study with a cross-sectional design. The sample consisted of 30 subjects who were household contacts of leprosy patients. Anti-PGL-1 IgM antibody levels were examined using the ELISA method at the Cito Laboratory, Yogyakarta.
Results: Regarding demographic characteristics, there were 18 female subjects (60%) and 12 male subjects (40%). LSQ+ results were found in 22 (73.3%) subjects, while LSQ- results were found in 8 (26.7%) subjects. The results of the anti-PGL-1 IgM examination were classified into three categories, namely seronegative (<605 U/ mL) totaling 25 people (83.3%), low titer seropositivity (605–1000 U/mL) totaling four people (13.3 %), and high titer seropositivity (>1000 U/mL) was one person (3.3%). The mean value of IgM anti-PGL-1 was 383.63 U/mL, with the lowest value being 0 and the highest being 1593 U/mL. Using Fischer's Exact showed no relationship between LSQ and IgM Anti-PGL-1 (p=0.287).
Conclusions: No relationship was found between LSQ and anti-PGL-1 IgM antibody levels in household contacts of leprosy patients. The results of the LSQ answers correlated with anti-PGL-1 IgM antibodies found in only five subjects.

Keywords: Household Contact, Leprosy, PGL-1, Questionnaire, Suspect.
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INTRODUCTION

Leprosy is a chronic granulomatous disease that mainly attacks the skin and peripheral nerves caused by the obligate intracellular pathogen *Mycobacterium leprae (M. leprae).* Based on clinical signs and symptoms, characteristics include loss of sensation in skin lesions, peripheral nerve swelling or pain, or the discovery of acid-fast bacilli in skin smears or skin biopsy.[1]

Leprosy and its clinical manifestations are the result of a dynamic interactive process between *M. leprae* and the cell-mediated immunity (CMI) of genetically predisposed subjects,[2] but various studies show that there are several other risk factors, such as living in the same house as a leprosy patient, living in an area endemic or hyperendemic leprosy, poverty, living in high-density households with more than two people sleeping together in one room, poor nutrition, poor sanitation or lack of clean water, and minimal availability of health services that increase an individual's risk or predisposition to developing this disease.[3,4]

Contacts who live in the same house as untreated multibacillary leprosy (MB) leprosy patients have the highest risk of eventually contracting leprosy, especially if the contact persons in the same household are blood relatives of the leprosy patient.[1] The duration of contact influences the risk of suffering from leprosy. The behavior of sharing a bed with a leprosy patient can be a medium of contact to facilitate the transmission of leprosy.[5,6]

Based on WHO data in 2020, leprosy was reported in 127 countries. As many as 127,396 new cases were detected at 16.4 per million population. The highest proportion of global cases registered for treatment was around 61.1%, and 66.6% of new cases detected were in Southeast Asia. Brazil, India, and Indonesia reported 72.5% of registered cases, and 74.0% of new cases were detected. This data shows that Indonesia is the third largest contributor to new leprosy cases globally, with 11,173 cases worldwide. In North Sumatra, in 2020, there were 173 registered cases of leprosy; this leprosy case shows that there are still many transmission sources in the community.[7–9]

An active search strategy by providing the Leprosy Suspicion Questionnaire (LSQ) contains 14 simple questions about symptoms and signs associated with leprosy. This technique increases the chances of early diagnosis and treatment, avoiding disability and effectively stopping disease transmission. This questionnaire has proven to be a simple and inexpensive instrument for screening and identifying new cases of leprosy and increasing awareness of the signs and symptoms of leprosy.[10]

In research by Bernados Filho et al. regarding new leprosy screening in the CPP-Jardinopolis prison population in

Brazil using LSQ, followed by clinical evaluation, as well as serological examination, it was found that the results were that LSQ proved to be an essential screening tool for new cases of leprosy in the Brazilian CPP-Jardinopolis prison with the results of the new case detection ratio leprosy is 9.6%. Apart from that, LSQ is also a means of health education and a reminder of the signs and symptoms of leprosy found in the community.[10]

Developments in the field of leprosy research have discovered the chemical structure of an antigen, mainly phenolic glycolipid 1 (PGL-1), resulting in a revolution in serodiagnostics of leprosy, which can be found in armadillo tissue infected with *M. leprae*. Phenolic glycolipid 1 is a potent and specific *M. leprae* cell surface antigen. The PGL-1 antigen consists of a fatty component that can survive for an extended period after an intact bacillus has undergone degradation and elimination. Individuals who have positive anti-PGL-1 levels have up to an 8-fold higher risk of developing leprosy.[11]

The Leprosy Suspicion Questionnaire and examination of anti-PGL-1 IgM antibody levels are additional examination methods that may show potential for the detection of new cases of leprosy. The LSQ detects new cases of leprosy by providing simple questions regarding early clinical symptoms that can arise in leprosy, and examining anti-PGL-1 IgM antibody levels is a serological examination that can support the results of the LSQ answers to diagnose leprosy in the patient's household contacts leprosy.

Research on LSQ as a screening to identify new cases of leprosy and its relationship with IgM anti-PGL-1 antibody levels in household contacts of leprosy patients still needs to be improved. It has never been carried out in Indonesia. Based on this background, the author researched the relationship between LSQ and anti-PGL-1 IgM antibody levels in household contacts of leprosy patients.

METHODS

Study Design

This research is an observational analytical study with a cross sectional approach. This research will run from April 2022 to July 2023. This research was conducted at the Dermatology and Venereology Polyclinic, Prof. Hospital. Chairuddin Panusunan Lubis USU Medan, RSUD Dr. Pirngadi, and Haji Adam Malik Hospital Medan. Examine blood samples to check anti-PGL-1 IgM antibody levels using the ELISA method at the Cito Laboratory, Yogyakarta city.

Data Collection

The research sample consisted of 30 subjects with a population that met the inclusion criteria: living at least three months in the same house as a leprosy patient, willing to participate in the research by signing informed consent, and aged 5 to 59 years. The exclusion criteria are individuals who have previously been diagnosed with leprosy, individuals with diseases such as diabetes mellitus, stroke, thyroid disease, and Parkinson's, and those pregnant and breastfeeding.

Data Analysis

The data that has been collected was analyzed statistically. Data processing was carried out using univariate analysis to analyze the characteristics of one variable by conducting descriptive tests. Then, proceeded with bivariate analysis to analyze the relationship between research variables; in this case, the Fisher's Exact test was used to determine the relationship between the Leprosy Suspicion Questionnaire (LSQ) and anti-PGL-1 IgM antibody levels.

RESULTS

This research was conducted from September 2022 to July 2023 and was attended by 30 household contacts of leprosy patients who came for treatment at the Dermatology and Venereology Polyclinic, Prof. Hospital. Chairuddin Panusunan Lubis USU Medan, RSUD Dr. Pirngadi, and Haji Adam Malik Hospital Medan. All subjects met the inclusion criteria, and blood was drawn to determine the value of anti-PGL-1 IgM antibody levels and their relationship with LSQ. The demographic characteristics of the subjects are shown in full in Table 1.

The age group in this study was group 5—11 years old, as many as six subjects; 12—25 years old, as many as eight subjects; 26—45 years, as many as nine subjects; and 46—59 years old, as many as seven subjects. The average age of the subjects was 29.67 years, with the youngest being seven years old and the oldest 59 years old. The most common contact status in this study was sibling contact status. The status of siblings is brother, brother, sister, uncle and aunt.

Subjects who answered "yes" to ≥1 question were in the LSQ+ group, and those who answered "no" to 14 LSQ questions, including LSQ-. LSQ+ results were found in 22 (73.3%) subjects, while LSQ- results were found in 8 (26.7%) subjects.

The results of the IgM anti-PGL-1 examination were classified into three categories, namely: seronegative (<605

Table 1. Demographic characteristics of household contacts of leprosy patients

Demographic Characteristics	n = 30	%
Gender		
Male	12	40
Female	18	60
Age		
5—11	6	20.0
12—25	8	26.7
26—45	9	30.0
46—59	7	23.3
Mean (SD)	29.67 (15.97)	
Median (Min-Max)	29 (7—59)	
Contact Status		
Spouse	3	10.1
Parents	7	23.3
Child	5	16.6
Family	15	50.0

Table 2. Results of the Leprosy Suspicion Questionnaire (LSQ) examination on household contacts of leprosy patients

No	Parameters	Yes n (%)	No n (%)	Total n (%)
	LSQ+			22 (73,3)
	LSQ-			8 (26,7)
1.	Do you feel numbness in your hands and/or feet?	3 (10)	27 (90)	30 (100)
2.	Tenderness	11 (36.7)	19 (63.3)	30 (100)
3.	Is there a loss of sensation on the skin?	1 (3.3)	29 (96.7)	30 (100)
4.	Spotted on the skin?	4 (13.3)	26 (86.7)	30 (100)
5.	A stinging sensation?	3 (10)	27 (90)	30 (100)
6.	Lump on the skin?	3 (10)	27 (90)	30 (100)
7.	Nerve pain?	3 (10)	27(90)	30 (100)
8.	Swolen extrimities?	0 (0)	30 (100)	30 (100)
9.	Swollen face?	1 (3.3)	29 (96.7)	30 (100)
10.	Weakness in hands?	2 (6.7)	28 (93.3)	30 (100)
11.	It's hard to get dressed? Wearing glasses? Writing? Holding the pan?	1 (3.3)	29 (96.7)	30 (100)
12.	Weakness in the leg? Is it hard to wear a sandal?	2 (6.7)	28 (93.3)	30 (100)
13.	Loss of eye hair?	1 (3.3)	29 (96.7)	30 (100)
14.	Loss of Eyebrow?	1 (3.3)	29 (96.7)	30 (100)

Table 3. Results of anti-PGL-1 IgM examination

IgM Anti PGL-1	n = 30
Seronegative (<605 U/mL)	25 (83.3%)
Low titer seropositivity (605–1000 U/mL)	4 (13.3%)
High titer seropositivity (>1000 U/mL)	1 (3.3%)
Mean (SD), U/mL	383.63 (57,846)
Median (Min-Max), U/mL	323.5 (0–1593)

Table 4. Relationship between LSQ and IgM Anti-PGL-1 levels in household contacts of leprosy patients

LSQ	IgM Anti PGL-1		p
	Seropositive n (%)	Seronegative n (%)	
LSQ+	5 (22.7)	17 (77.3)	0.287a
LSQ-	0	8 (100)	

*Analysis was carried out using the Fisher Exact Test. The result was considered significant if the p-value ≤ 0.05.

U/mL) totaling 25 people (83.3%), low titer seropositive (605–1000 U/mL) totaling four people (13, 3%), and high titer seropositive (>1000 U/mL) was one person (3.3%). The mean value of IgM anti-PGL-1 was 383.63 U/mL, with the lowest value being 0 and the highest being 1593 U/mL found in 1 subject aged seven years. The percentage of anti-PGL-1 IgM examination results was 16.6%. The results of this examination showed that out of 30 household contacts of leprosy patients, five people with seropositive results were more likely to develop leprosy than contacts with seronegative results.

Table 4 presents the analysis of the relationship between LSQ and IgM Anti-PGL-1 levels in household contacts of leprosy patients.

Of the 22 contacts with LSQ+ results, five people (22.7%) had IgM anti-PGL-1 seropositive results. Meanwhile, all eight contacts with LSQ- results had IgM anti-PGL-1 seronegative results. Fischer's Exact test showed no relationship between LSQ and IgM Anti-PGL-1 (p=0.287).

DISCUSSION

This study is the first to link LSQ with IgM Anti-PGL-1 in household contacts of leprosy patients. Research on LSQ is currently still limited. In one study of the LSQ in prison populations in Brazil by Filho et al. (2020), namely from 1,400 subjects, 187 subjects obtained LSQ+ results. Then, following up with clinical evaluation and laboratory examination, 18 subjects were diagnosed with leprosy, with an NCDR rate of 9.6%. Serological examination of anti-PGL-1 IgM antibodies was also examined, with anti-PGL-1 IgM seropositive levels of 20.3% of 1,227 subjects.[10] This study was a prospective clinical analysis study to find new cases of leprosy and did not link LSQ with examination of anti-PGL-1 IgM antibody levels.

There were 18 female subjects (60%) and 12 male subjects (40%). This is the same as research by Priyadharsini et al. (2022), where the number of household contacts of leprosy patients was more female, namely 22 (52.4%) subjects and 20 (47.6%) male subjects.[12] Rahfiludin et al. (2012), among leprosy patient contacts, there were also more female subjects, namely 72.4%.[13]

According to the literature, most cases of leprosy are found in the age group between 20—and 30 years.[14] Leprosy can occur at any age; in Lubis RD et al. (2021) research, the most common age group is the 15 age group—≤ 24 years old. This age group has the highest number of seropositive subjects compared to other age groups.[15]

Another study regarding LSQ was in populations of endemic areas in the interior of Sao Paulo, Brazil, by Filho et al. (2021); LSQ was distributed to 3,241 subjects, LSQ+ results were obtained

in 300 subjects who were followed up with clinical evaluation and laboratory examination, 60 subjects were diagnosed with leprosy, NCDR 20%. Examination of anti-PGL-1 IgM levels was seropositive in 33.4% of the 479 subjects examined.[16] This study analyzed immuno epidemiological aspects to confirm leprosy in endemic areas in Sao Paolo, Brazil and did not correlate LSQ with an examination of anti-PGL-1 IgM antibody levels.

In Table 1, the most common complaint felt by subjects was tingling (prickling) in 11 subjects (36.7%), followed by complaints of skin spots in 4 subjects (13.3%). Complaints of numbness in the hands and feet, stinging sensation, nodules on the skin, and nerve pain were present in 3 subjects (10%). Complaints of weakness in the hands and weakness in the feet, such as difficulty wearing sandals, were felt by two subjects each (6.7%). Complaints of loss of sensation on the skin, swollen face, difficulty buttoning clothes, eyelashes falling out, and loss of eyebrows were reported by one subject each (3.3%). Complaints of swollen hands and feet in the subjects answered 0, which means there were no such complaints in the subjects of this study.

In previous research conducted by Filho et al. (2020) in the prison population in Sao Paolo, Brazil, with the LSQ instrument, the most common answers were the same as in this study, namely tingling symptoms (prickling), which was 41.2% and the second most common spot on the skin at 38.5%.[10] Other studies with the LSQ instrument conducted by Filho et al. (2021) in a population of endemic areas in Brazil had the same results, namely that the most common complaint was tingling (prickling) at 11.8%, and the second most common was spots on the skin at 10.7%.[16]

Tingling and numbness are early signs of nerve damage in leprosy. It is necessary to educate household contacts so they do not ignore these complaints and report them to health officials for further examination. Signs and symptoms of tingling are often gradual and progressive in leprosy patients, accompanied by visible muscle weakness, ultimately forming leprosy deformities.[6]

In this study, four research subjects complained of skin spots, and one was diagnosed with leprosy after further examination. Spots on the skin can be hypopigmentation and hyperpigmentation. Hypopigmented spots are often considered tinea versicolor and ignored by household contacts of leprosy patients. Spots on the skin can be an early sign of leprosy.[17] However, it needs to be differentiated from pityriasis versicolor and other pigmentation diseases with further examination by a health worker.

Other complaints, such as stinging sensations, nodules on the skin, and nerve pain, were found in each of the three subjects. This usually occurs in patients who experience leprosy reactions. However, it can also be an early sign of leprosy symptoms. Nerve pain, or neuritis, is defined as pain that begins or is caused by disease, lesion, or primary dysfunction in the peripheral or central nervous system (CNS). In leprosy, neuritis can occur due to the invasion of Schwann cells and axons by *M. Leprae*, which causes demyelination and axonal degeneration. This presents a broad spectrum of symptoms, including paresthesia, dysesthesia, hyperesthesia, and allodynia along the nerves and in the affected area, which can be very bothersome.[18] Skin nodules are one of the clinical symptoms of leprosy, seen in tuberculoid and lepromatous types of leprosy. One form of leprosy with papules and nodules is histoid leprosy, which has a higher bacilli load than ordinary lepromatous leprosy, showing shiny and diffuse nodules and papules, as well as varying degrees of skin infiltration. Forms of leprosy lesions in the form of papules and other nodules can be found in erythema nodosum leprosum (ENL).[1]

Weakness in the hands, such as difficulty buttoning clothes, difficulty writing, and weakness in the feet, such as difficulty wearing sandals, are early manifestations of neuritis. If these symptoms persist, motor paralysis can occur in leprosy patients. In leprosy, tendon reflexes are expected because the CNS is usually uninvolved. However, in severe neuritis, some patients may show abnormal tendon reflexes.[19]

Swollen hands and feet and swollen faces are rheumatological symptoms of leprosy. A study by Wakhlu et al. (2018) found that 20.6% of leprosy patients had symptoms of swelling in the hands and feet. Most of them were diagnosed with pure leprosy neuritis. In this study, it was stated that swelling of the hands and feet in leprosy is a rheumatological manifestation of leprosy, either as a disease process or a manifestation that arises from leprosy.[19]

Eyelash loss and loss of eyebrows were each complained of by one subject. Lepromatous leprosy can disrupt hair growth, causing loss of eyebrows and eyelashes early in the disease, with the development of characteristic leonine facies. Bilateral loss of eyebrows and eyelashes is seen in around 9.3—36.5% of patients with lepromatous leprosy. In a cross-sectional study of 23 patients, trichoscopy findings included reduced hair density, multiple vellus hairs, and distorted skin pigmentation in leprosy patients.[20]

Serological tests based on antibodies to PGL-1 have been widely used to support the diagnosis of leprosy, especially for leprosy cases with doubtful signs and symptoms in efforts to eradicate leprosy.[21] These antibody levels show a linear relationship between the bacterial index, which is a marker of serum bacterial load in leprosy patients.[22] Literature states that seropositive results show a 7.2 times higher risk of developing leprosy than seronegative contacts, especially in the MB form of leprosy which is 24 times higher for developing leprosy. Seropositive individuals should be followed up on, although not all seropositive individuals will develop the disease.[23]

The leprosy suspicion questionnaire serves as a simple, cost-effective means of leprosy screening, triggers awareness of the signs and symptoms of leprosy among leprosy patient contacts, and is recommended in leprosy screening measures in research conducted in Brazil.[10,16] Increased risk of leprosy ten times compared to LSQ- subjects.[16]

Phenolic glycolipid 1 is a specific antigen of *M. leprae,* which can cause an antibody response in the body. It has been proven to be very useful in leprosy patients. Household contacts of leprosy patients.[24] Positive levels of anti-PGL-1 IgM antibodies are a biomarker for detecting the presence of *M. leprae* and carrying the risk, which is higher for the

development of leprosy.[10]

The leprosy suspicion questionnaire and anti-PGL-1 IgM antibody levels are additional screening methods that may show potential for leprosy detection. However, this study found no relationship between the two examination methods. This study still has several limitations, namely, it did not include any compounding variables that might have affected the result of the study.

CONCLUSION

No relationship was found between LSQ and anti-PGL-1 IgM antibody levels in household contacts of leprosy patients. The results of the LSQ answers correlated with anti-PGL-1 IgM antibodies found in only five subjects. The results of the answers to the LSQ questionnaire were more often found in the LSQ+ group, namely 22 subjects. Household contacts of leprosy patients are more often found in the age group 26-45 years and female. Further studies are needed to validate this finding.

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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ETHICAL CONSIDERATION

This research has obtained ethical clearance with letter number 1224/KEPK/USU/2022 from the Research Ethics Commission of the Faculty of Medicine, University of North Sumatra.

AUTHOR CONTRIBUTION

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting, and approval for publication of this manuscript.

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