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Assessment of Fertility Status among Multibacillary Leprotic Females in Kafr El-Shiekh and Damietta Governerates

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ABSTRACT

Background: Leprosy is a chronic infectious disease caused by obligate intra- cellular microorganism mycobacterium leprae that tend to infect skin and the peripheral nerves. The disease manifested clinically by a spectrum depending on the host immune response and finally leading to peripheral nerve damage and deformities. Although leprosy rarely involves the female genital tract, a significantly larger number of female patients with MB leprosy had irregular periods postdating the onset of leprosy also gonadotropic hormone levels were elevated in significantly more patients with MB and that the mean levels of these hormones showed an increasing trend from controls.

Objective: The objective of this study is to assess the fertility status among multibacillary leprotic females

Patients and Methods: This study was conducted on thirty multibacillary leprotic females who were selected from Kafr-Elsheikh dermatology and leprosy hospital and Damietta dermatology and leprosy hospital and twinty healthy females as a control group. Patients were subjected to history taking, general clinical examination and dermatological examination, and were divided into groups according to WHO classification.

Results: Our study showed that a significantly large number of female patients with MB leprosy had irregular period post dating to the onset of leprosy and the gonadotrophic hormone level is significantly elevated in patients than in control in addition to fertility which is significantly affected in MB leprotic females.

Conclusion: the findings of this study are significant in view of the fact that it is generally believed that ovarian dysfunction does not occur in leprosy. Even in the absence of confounding factors like anemia and tuberculosis, leprosy may be associated with menstrual irregularities, infertility, and elevation of gonadotropin hormones.

Keywords: Leprosy, fertility, follicle-stimulating hormone, luteinizing hormone.

INTRODUCTION

Leprosy, known as Hansen's disease (HD),is a chronic granulomatous infectious disease caused by the obligate intracellular microorganism mycobacterium leprae that tend to infect skin and peripheral nerves. Nerve damage seen across the spectrum is the main cause of deformities and morbidity in this disease [(1)].

HD is still considered a major health problem in some countries of Asia, Latin America and Africa including Egypt. According to World Health Organization (WHO), 228,474 new leprosy cases was detected worldwide during 2010 as reported by 130 countries [(2)].

The Ridley-Jopling classification of leprosy is based on clinical and histopathological criteria , which suggest a disease spectrum with five clinical categories : tuberculoid (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL) and lepromatous leprosy (LL)*(3)*. At one pole, TT leprosy is characterized by few well-defined skin patches, few bacilli (paucibacillary; PB) and vigorous cell-mediated immunity (CMI) [(4)]. At the other pole ,LL present with many skin lesion with uncontrolled proliferation of leprosy bacilli (multibacillary ;MB), an inefficient CMI [(5)]. Borderline leprosy manifests clinical and immunological features with characteristics between the two forms [(6)].

Traditionally, a male-over-female preponderance has been reported in various epidemiological studies [(7)].

Traditional beliefs, the low status assigned to women, and women's limited mobility, illiteracy, and poor knowledge of leprosy have been suggested as important sociocultural factors responsible for underreporting of cases of women affected with leprosy [(8)]. A significant number of female patients with MB leprosy had irregular periods postdating the onset of leprosy than patients with PB leprosy. Also gonadotropic hormone levels were elevated in significantly more patients with MB leprosy than patients with PB leprosy, and that the mean levels of these hormones showed an increasing trend from controls to patients with PB to patients with MB leprosy [(9)].

AIM OF THE WORK

Evaluation of fertility status among multibacillary leprotic females.

PATIENTS AND METHODS

The current study is a case control study which was carried on 30 leprotic females (as a

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patient's group), and 20 apparently healthy females (as a control group). Patients were recruited from Kafr-Elsheikh dermatology and leprosy hospital and Damietta dermatology and leprosy hospital between the periods from November 2017 to July 2018.

Ethical consideration

An informed consent was obtained from all participants in the study after approval of Research Ethics Committees of Faculty of Medicine, Al-Azhar University, Kafr-Elsheikh dermatology hospital. Each participants was informed about the nature of the procedure and agreed that their data could be used anonymously for research.

Classification

Patients were divided into: Group(A):included 30 MB leprotic female patients , who were newly diagnosed to have leprosy. Group(B) **:**Control group included: 20 apparently healthy age and sex matched female volunteers. Controls were selected from attendants of Kafr-Elsheikh dermatology hospital and Damietta dermatology hospital for cosmetic purposes, not relative to leprosy patients and follow the same exclusion criteria. The patients were selected according to the following inclusion and exclusion criteria:

Inclusion Criteria: Leprosy patients with age group ranged between 19-35 years. Early diagnosed female patient in the fertile age.

Exclusion Criteria: Patients above 35years old or below 19 years old. Confounding conditions for menstrual irregularities, like anemia ,anti- cancer chemotherapy/radiotherapy, thyroid disorders. Another cause of infertility as polycystic ovaries or under any contraceptive methods. Other chronic infectious diseases. Other granulomatous disease (tuberculosis, sarcoidosis).

The patients were subjected to: Detailed history taking. Clinical examination. Laboratory investigation.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20. 0**. (**Armonk, NY: IBM Corp**)** Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.
The used tests were:

1- Chi-square test

For categorical variables, to compare between different groups.

2- Fisher's Exact or Monte Carlo correction

Correction for chi-square when more than 20% of the cells have expected count less than 5.

3- Student t-test

For normally distributed quantitative variables, to compare between two studied groups.

4- Mann Whitney test

For abnormally distributed quantitative variables, to compare between two studied groups.

RESULTS

The current study included 30 leprotic female patients . Their ages ranged from 19-35 years with a mean age of 28. 07 years(± 4. 16) and 20 healthy female volunteers as a control group. Their ages ranged from 21– 35 years with a mean age of 26. 45 years (± 3. 78).

The patients were matched regarding age and marital status with no statistically significant difference(P>0. 05)

Table (1): Comparison between the two studied groups according to demographic data

	MB leprotic cases (n= 30)		**Control (n= 20)**		**P**
	No.	**%**	**No.**	**%**	
Marital status					
Married	27	90. 0	13	65. 0	0. 067
Unmarried	3	10. 0	7	35. 0	
Age (years)					
Min. – Max.	19. 0 – 35. 0		21. 0 – 35. 0		
Mean ± SD.	28. 07 ± 4. 16		26. 45 ± 3. 78		0. 169
Median	28. 50		26. 50		

χ^2: **Chi square test** t: **Student t-test**
p: p value for comparing between the two groups

Table (2): Distribution of the studied cases according to onset of the disease in MB leprotic cases (n= 30)

Onset of the disease (months)	No.	%
<5	4	13. 3
≥5	26	86. 7
Min. – Max.	3. 0 – 9. 0	
Mean ± SD.	6. 30 ± 1. 68	
Median	6. 0	

Table (3): Comparison between the two studied groups according to menstruation

Menstruation	MB leprotic cases (n= 30)		Control (n= 20)		^{FE}p
	No.	%	No.	%	
Regular	21	70. 0	20	100. 0	0. 007*
Irregular	9	30. 0	0	0. 0	

χ^2: **Chi square test** FE: **Fisher Exact**
p: p value for comparing between the two groups
*: Statistically significant at $p \leq 0.05$

The difference between cases and the control is statistically significant (p-value = 0. 007).

Table (4): Comparison between the two studied groups according to fertile / infertile.

Fertile / Infertile	MB leprotic cases (n= 30)		Control (n= 20)		^{MC}p
	No.	%	No.	%	
Fertile	23	76. 7	13	65. 0	
Infertile	4	13. 3	0	0. 0	0. 039*
Unmarried	3	10. 0	7	35. 0	

χ^2: **Chi square test** FE: **Fisher Exact**
p: p value for comparing between the two groups
*: Statistically significant at $p \leq 0.05$

The difference between cases and the control was statistically significant (P-value=0. 039)

Table (5): Distribution of the studied cases according to Fertile / Infertile in MB leprotic cases (n= 30)

Fertile / Infertile	No.	%
Fertile	23	76. 7
Infertile	**4**	**13. 3**
1ry	1	3. 3
2ry	3	10. 0
Unmarried	3	10. 0

Number of infertile cases is 4(13. 3%) with one case(3. 3%) with 1ry infertility and 3(10. 0%)cases with 2ry infertility.

Table (6): Comparison between the two studied groups according to hormone estimated

Hormone estimated	MB leprotic cases (n= 30)	Control (n= 20)	U	P
FSH				
Min. – Max.	4. 90 – 19. 65	4. 80 – 7. 15	178. 50*	0. 016*
Mean ± SD.	8. 03 ± 4. 17	6. 01 ± 0. 78		
Median	6. 66	6. 02		
LH				
Min. – Max.	2. 19 – 8. 95	2. 27 – 3. 80	192. 0*	0. 032*
Mean ± SD.	3. 77 ± 1. 84	2. 90 ± 0. 43		
Median	3. 19	2. 85		
Prolactin				
Min. – Max.	6. 90 – 40. 25	6. 58 – 21. 50	177. 50*	0. 015*
Mean ± SD.	18. 58 ± 8. 88	13. 20 ± 4. 69		
Median	17. 10	13. 75		

U: **Mann Whitney test**, p: p value for comparing between the two groups, *: Statistically significant at $p \leq 0.05$

The difference between cases and the control regarding FSH hormone is statistically significant (p-value =0. 016).
The difference between cases and the control regarding LH hormone is statistically significant (p-value =0. 032).
The difference between cases and the control regarding Prolactin hormone is statistically significant (p-value =0. 015).

Table (7): Relation between menstruation and hormone estimated disease in MB leprotic cases (n= 30)

Hormone estimated	Menstruation		U	P
	Regular (n= 21)	Irregular (n= 9)		
FSH				
Min. – Max.	4. 90 – 19. 65	5. 20 – 19. 65		
Mean ± SD.	6. 92 ± 3. 03	11. 97 ± 6. 01	36. 50*	0. 007*
Median	6. 10	7. 91		
LH				
Min. – Max.	2. 38 – 8. 95	3. 14 – 8. 95		
Mean ± SD.	3. 26 ± 1. 35	5. 69 ± 2. 45	18. 50*	0. 001*
Median	2. 88	4. 0		
Prolactin				
Min. – Max.	6. 90 – 40. 25	8. 55 – 40. 25		
Mean ± SD.	16. 05 ± 6. 76	27. 07 ± 11. 48	34. 0*	0. 006*
Median	15. 40	22. 30		

U: **Mann Whitney test**
p: p value for association between menstruation and hormone estimated disease
*: Statistically significant at $p \leq 0.05$

The difference between FSH in cases with regular menstruation and those with irregular menstruation is statistically significant (p-value =0. 007).
The difference between LH in cases with regular menstruation and those with irregular menstruation is statistically significant (p-value =0. 001).
The difference between Prolactin in cases with regular menstruation and those with irregular menstruation is statistically significant (p-value =0. 006).

Table (8): Relation between Fertile / Infertile and hormone estimated disease in MB leprotic cases (n= 27)

Hormone estimated	Fertile / Infertile		U	P
	Fertile (n= 23)	Infertile (n=4)		
FSH				
Mean ± SD.	7. 34 ± 1. 56	15. 81 ± 5. 81		
Median	6. 10	18. 20		
LH				
Mean ± SD.	3. 53 ± 1. 57	7. 33 ± 2. 26		
Median	2. 95	8. 18		
Prolactin				
Mean ± SD.	18. 15 ± 7. 10	34. 84 ± 8. 95		
Median	17. 40	38. 80		

U: **Mann Whitney test**

p: p value for association between Fertile / Infertile and hormone estimated disease

*: Statistically significant at $p \leq 0.05$

The difference between FSH in the fertile group and the infertile group is statistically significant (p-value =0. 015).

The difference between LH in the fertile group and the infertile group is statistically significant (p-value =0. 005).

The difference between Prolactin in the fertile group and the infertile group is statistically significant (p-value =0. 006).

DISCUSSION

Leprosy, or Hansen's disease (HD), is an ancient bacterial disease that, although curable, continues to be a significant health problem in many parts of the world. HD results from infection with the Mycobacterium leprae bacillus, which produces a chronic infection in humans that affects mainly peripheral nerves and skin and produces a spectrum of clinical phenotypes [(10)].

Leprosy is a multisystem infection in which leprosy granulomata are demonstrated in several organs, including testes, liver, adrenals, lymph nodes, and bone marrow. The involvement of testes in leprosy is not uncommon and manifests initially as sterility due to involvement of the germinal cells and later as impotence. However, there is a paucity of data on the involvement of female reproductive organs in leprosy. Of the studies available, there is contradictory evidence on the effect of leprosy on menstrual function and fertility [(11)].

Our study was conducted on thirty multibacillary leprotic females who are newly diagnosed . All cases undergo assessment of hormonal profile for FSH ,LH and prolactin on third day of menstruation in addition to ultrasound (vaginal for married and abdominal for unmarried females) for assessment of the ovarian status .

Our results showed that nine of these thirty patients had irregular period post dating to the onset of leprosy . Of the twenty seven married females ,four cases are infertile ;of these 3 have secondary infertility and one case has primary infertility. Three patients who had infertility also had elevated levels of FSH and LH and prolactin . The mean levels of FSH ,LH and prolactin were significantly higher in patients with multibacillary leprosy than the controls. This study was in agreement with study done by ***Khanna et al.*** on 229 female patients . Their patients are classified into 79 (34. 5%) in the PB group and 150 (64. 5%) in the MB leprosy. The study found that the number of cases with irregular period post-dating onset of leprosy was 39 (26%) in MB females and 5 (6. 3%)in PB females and the difference between both was statistically highly significant ($P < 0.001$). Also when they compared the fertility profile of the patients with irregular periods, though 10% of the patients with MB leprosy had not been able to conceive in contrast to only 2. 5% of patients with PB leprosy, this difference was not statistically significant ($P > 0.05$). With measuring the levels of FSH, LH, and prolactin in all patients with leprosy and 100 age-matched controls, they found that one (1. 3%) of the 79 patients with PB and 14(9. 3%) of the 150 patients with MB leprosy had elevated gonadotropin levels, and this difference was statistically significant ($P < 0.05$). The mean levels of LH, FSH, and prolactin were highly significantly elevated in patients with MB leprosy compared with controls [(9)].

It also correlate with an earlier study on 86 female patients with MB leprosy, they noted that 26(30%) of patients had irregularities of periods post-dated the onset of leprosy. Of the 24 married women, 12 (50%) were infertile; of these 7 (29. 1%) had primary infertility and 5 (20. 8%) had secondary infertility, The 12 patients, with irregular periods who had children, had conceived before their periods had become irregular. Seven (29. 1%) patients who had infertility also had elevated levels of FSH and LH almost reaching castration levels. The mean levels of FSH and LH were significantly higher in patients with multibacillary leprosy compared with the controls [(12)].

Sharma et al. in a recent study of 35 adult female patients with bacillary positive leprosy,

found that leprosy had no direct effect on menarche, menstrual cycle, fertility, and menopause. Significantly, 3 (8. 57%) of their lepromatous leprosy patients had never conceived [13].

Also Bogush reported menstrual dysfunction in their patients with leprosy and observed that the early institution of therapy could prevent this. However, he did not comment on the fertility status of his patients and the hormonal profile was not evaluated as well [11].

Another study done by ***Fleger et al.*** [14] found that 54% of female patients with leprosy were sterile, and ***King and Marks***[15] reported gross menstrual abnormalities in patients with leprosy. In none of these studies was the hormonal profile evaluated . Also ***Hardas et al.*** noted that though pregnancy alters the course of leprosy, leprosy does not have any effect on menstrual cycle or fertility. Interestingly, in only 18% of patients from that study did the endometrial biopsy taken in the premenstrual period show a secretory phase, indicating some hormonal imbalance [16].

Mitsuda and Ogawa, in a study of one hundred and fifty autopsies on cases of leprosy, demonstrated lepra cells in the endometrium, fallopian tubes, and vaginal mucosa of female patients with LL, he noted that leprosy does not cause infertility [17].

In our study ultrasound (vaginal for married and abdominal for unmarried females)was done and it was normal for all cases .

Our study is with the agreement of studies done by ***Khanna et al.*** ensure that ovarian dysfunction does not occur in leprosy [9].

Another study by ***Bernard and Vazquez*** [18] for assessment of ovarian function in leprotic females , found that affection of the ovaries is rare and in those in which histopathology was performed, the ovaries were not involved [19].

In contrast to a study done by ***Bonar and Rabson*** [20] found that, although leprosy rarely involves the female genital tract ,the ovary is the most commonly involved gynecologic site . In one well documented case, microscopic examination of the grossly normal ovaries revealed numerous vacuolated histiocytes within the ovarian stroma that contained Mycobacterium leprae. In chronic forms of leprous oophoritis, a chronic inflammatory cell infiltrate and fibrosis are seen, and bacilli usually are demonstrable [21].

CONCLUSION

The findings of this study are significant in view of the fact that it is generally believed that ovarian dysfunction does not occur in leprosy. Even in the absence of confounding factors like anemia and tuberculosis, leprosy may be associated with menstrual irregularities, infertility, and elevation of gonadotropin hormones.

REFERENCES

1. **Scollard DM, Adams LB, Gillis TP *et al.* (2006):** The continuing challenges of leprosy. Clin Microbiol Rev., 19:338-381.
2. **WHO (2011):** Global leprosy situation, leprosy update, Wkly epidemiol Rec., 86:389-400.
3. **Ridley DS and Jopling WH (1966):** Classification of leprosy according to immunity: A five-group system. Int J Lepr Other Mycobact Dis., 34(3):255-273.
4. **Fitness J, Tosh K, Hill AV (2002):**Genetics of susceptibility to leprosy. Genes Immunol., 3:441-453.
5. **Britton WJ and Lockwood DN (2004):** Leprosy. Lancet, 363:1209–1219.
6. **Sasaki S**, **Takeshita F, Okuda K, Ishii N (2001):** Mycobacterium leprae and leprosy: acompendium. Microbiol Immunol., 45:729-736.
7. **Van Veen NH, Miema A, Richardus JH (2006):** The relationship between detection delay and impairment in leprosy control: a comparison of patients cohorts from Bangladesh and Ethiopia. Lepr Rev., 77(4): 356-365.
8. **Padhi T and Pradhan S (2015):** Family motivation card: An innovative tool for increasing case detsction in a resource poor setting. Lepr Rev., 86(2): 170-175.
9. **Khanna N, Singh M, Rasool S *et al.* (2014):** Menstrual irregularities, fertility status, and ovarian functionin female patients with leprosy in India. Int J of Dermatol., 53: 1114–1118.
10. **Polycarpou A, Walker SL, Lockwood DNJ (2013):** New findings in the pathogenesis of leprosy and implications for the management of leprosy. Curr Opin Infect Dis., 26**:**413–419.
11. **Bogush TG (1979):** The question of the menstrual function in women with lepromatous leprosy before pubescence. Sci Works Lepr Res Inst., 9: 116–118.
12. **Neena K, Ammini AC, Singh M, Pandhi KR (2003):** Ovarian function in female patients with multibacillary leprosy. Int J of leprosy, 71(2):101-5.
13. **Sharma P (1996):** Disabilities in multibacillary leprosy patients: before, during and after multidrug therapy. Indian J Lepr.,68: 127–136.
14. **Fleger J, Biric B and Prica S (1963)**: Importance of leprosy in gynaecology and midwifery. Trop Dis Bull., 60 :446-447.
15. **King JA and Marks RA (1958):** Pregnancy and leprosy. Am J Obstet Gynaecol., 76: 438-442.
16. **Hardes U, Survey R, Chakravarty D (1972):** Leprosy in gynecology and obstetrics. Int J Leprosy Other Mycobact Dis., 40(4):399-401.
17. **Mitsuda K and Ogawa M (1937):** A study of one hundred and fifty autopsies on cases of leprosy. Int J Leprosy Other Mycobact Dis., 5:53-60.
18. **Bernard JC and Vazquez CA (1973):** Visceral lesions in lepromatous leprosy. Study of sixty necropsies. Int J Lepr Other Mycobact Dis., 41: 94-101.
19. **Foss NT and Motta AC (2012):** Leprosy, a neglected disease that causes a wide variety of clinical conditions in tropical countries. Mem Inst Oswaldo Cruz, Rio de Janeiro, 107: 28-33.
20. **Bonar BE and Rabson AS (1957):** Gynecologic aspects of leprosy. Obstet Gynecol., 9:33–43.
21. **Julie AI and Philip BC (2011):** Blaustein's Pathology of the Female Genital Tract: Nonneoplastic Lesions of the Ovary. Springer-Verlag New York; pp 597-645.