

Risk factors for buruli ulcer in a referral mission hospital in anambra state, Nigeria: A case control study

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ABSTRACT

Aims: Buruli ulcer is a chronic debilitating skin disease believed to be caused by an environmental bacterium – *Mycobacterium ulcerans*. Its mode of transmission is still elusive. Buruli ulcer can cause permanent disability and deformity which may severely limit a person's ability to carry out normal daily activities. The associated stigma may greatly restrict the social participation by affected persons. Though early detection and adequate medical and surgical treatment can minimize future disability and complication, recognizing the risk factors of this disease can lead to adoption of appropriate preventive strategies. **Methods:** A case-control study of 120 patients (40 cases and 80 matched controls) was undertaken in a referral mission hospital. A structured questionnaire was used to collect data from subjects. The folders of case subjects were also reviewed. **Results:** Significantly higher proportion of Buruli ulcer cases were males when compared to the control group ($x^2 = 3.84$, $p = 0.05$, $OR = 2.22$). Poor education ($x^2 = 14.27$, $p=0.0003$ and $OR = 5.13$), visit to water bodies ($x^2 = 67.78$, $p=0.00000$ and $OR = 63$), No BCG

vaccination ($x^2 = 6.79$, $p=0.01$ and $OR = 2.79$), pet in the house ($x^2 = 9.25$, $p=0.002$ and $OR = 3.55$), poor drinking water source ($x^2 = 45.32$, $p=0.00000$ and $OR = 19.52$), no preventive measure ($x^2 = 18.3$, $p=0.0005$ and $OR = 6.27$) were significantly associated with Buruli ulcer. **Conclusion:** This study identified, regular visit to water bodies, male gender, poor education, lack of Bacille Calmette Guerin (BCG) vaccination and poor drinking water source as risk factors for Buruli ulcer, in the face of apparent lack of awareness of disease and its risk factors among the subjects. Aggressive public enlightenment is recommended to hopefully reduce the prevalence of Buruli ulcer disease.

Keywords: Buruli ulcer, Nigeria, Risk factors

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INTRODUCTION

Buruli ulcer (BU) is a chronic debilitating skin disease caused by *mycobacterium ulcerans*. It is an acid-fast bacillus and belongs to the same family of organisms that cause tuberculosis and leprosy. The mode of *mycobacterium ulcerans* transmission is not fully understood although the disease is known to be linked

to contaminated water. Areas affected by buruli ulcer disease are located near stagnant or slow moving waters.

Buruli ulcer is one of neglected tropical diseases and has been observed more frequently during the rainy season in Africa and exposure may occur in muddy farming fields. Transmission of the organism is probably via skin trauma [1,2]. Insects may also play a role in some cases, though not in all foci where transmission occurs. Water insects (Naucoris and Belostomaspp) have been implicated in laboratory transmission of infection but their potential role as vectors has been questioned by studies in west Africa [3]. In Australia, salt marsh mosquitoes appear to have positive polymerase chain reaction signals [4]. Intermediate hosts including aquatic animals may also play a role. Amoebae have also been implicated but their role in transmission is limited. Human to human transmission is rare.

The disease manifests itself as papule, nodules, plaques, ulcers and oedematous areas of the skin. Buruli ulcer often starts as a painless swelling (nodules). It can also initially present as a large painless area of induration (plaque) or a diffuse painless swelling of the legs, arms or face (oedema) [5]. The local immunosuppressive properties of the mycolactone toxin enable the disease to progress with no pain and fever. Without treatment or sometimes during antibiotic treatment the nodules, plaques or oedema will ulcerate within four weeks with the classical undermined borders. Occasionally bones are affected causing gross deformities [5]. The distinctive features of a buruli ulcer include undermining edges, white cotton wool-like appearance and thickening and darkening of the skin surrounding the lesion [5].

In a known endemic area, diagnosis of buruli ulcer can be made based on clinical observation that considers clinico-epidemiological features which indicate that most cases are in children under 15 years of age, about 85% of lesions are on the limbs and lower limb lesions are twice as common as upper limb lesions. In addition to the clinical diagnosis, at least one of the following laboratory findings is required to confirm the diagnosis of buruli ulcer: Acid-Fast Bacilli (AFB) in a smear stained by the Ziehl-Neelsen technique, histopathological study of a biopsy specimen showing typical necrosis and acid-fast bacilli, positive polymerase chain reaction (PCR) test for mycobacterium ulcerans and positive culture of mycobacterium ulcerans [6].

In spite of the seeming high prevalence of buruli ulcer, the disease remains generally poorly understood. Diagnosis is largely presumptive and the associated risk factors poorly defined. This study is aimed at identifying possible risk factors for buruli ulcer in the study area. It also determines the knowledge of buruli ulcer among the respondents and explores preventive measures adopted by the affected subjects.

MATERIALS AND METHODS

Study design and case definition

A case-control study was designed in a mission hospital located in Anambra state, Nigeria and classified as a secondary healthcare facility. It is a referral centre for buruli ulcer disease and is largely supported by German Leprosy and Tuberculosis Relief Association.

Ethical consideration

Ethical approval for the project was obtained from the NAUTH Ethics Committee through the office of the Head of Department, Community Medicine and PHC, Nnamdi Azikwe University Teaching Hospital, Nnewi, Nigeria. Appropriate permission was also obtained from the Manager of the Mission hospital and heads of various sections of the records department. The nature of the study was clearly explained to them before obtaining the approval. Adequate confidentiality was maintained during the use of the patient's folder. Verbal informed consents were obtained from the subjects.

Study population

The study population consists of 40 patients diagnosed with buruli ulcer. All the patients with suspected buruli ulcer that were referred to the centre and examined by the Physician in charge of buruli ulcer disease and confirmed by laboratory tests using Ziehl-Neelsen technique and Polymerase Chain Reaction (PCR) test. The control population consists of persons not diagnosed of buruli ulcer disease or similar illness but who share similar socio-demographic and geographical characteristics as the cases. The control population was selected to be of the same sex and age range of ± 2 SD with the case (study) population.

Selection Criteria for Subjects

Inclusion criteria for case: 1) Patients diagnosed with Buruli ulcer and have been confirmed by Polymerase Chain Reaction.

Exclusion criteria: Those whose ulcer have not been confirmed.

Sample Size Determination

$$X = \frac{U\sqrt{\pi_1(1-\pi_1)+(1-\pi_2)} + v\sqrt{[\pi(1-\pi)]}}{(\pi_1 - \pi_2)^2}$$

U = 1.28 (where power is 90%).

V = 1.96 (where significance level = 5%).

π_1 = Proportion of control exposed.

π_2 = Proportion of cases exposed.
It can also be calculated from,

$$\pi_2 = \frac{\pi_1 OR}{1 + \pi_1 (OR - 1)}$$

Where OR = Odds ratio; $\pi_1 = 0.1$; $\pi_2 = 0.25$
 $X = 57.30 \approx 60$; Minimum sample size = $2X = 120$.

Sampling Method

A convenience sampling method was used to collect data for the calculated sample size. The folders of 40 patients diagnosed of Buruli ulcer were assessed through the hospital register. Using the folder numbers, the patients' records were traced and vital information required for the research was collected. The patients were also identified for primary data collection using interviewer administered questionnaires.

The control groups 80 subjects consisted of apparently normal persons of similar sex, age and geographical location attending the hospital or live within the region where the patients reside. The same questionnaires were administered on the control. The data was collected using an interviewer-administered questionnaire. This was used to collect data on socio-demographic characteristics, other relevant risk factors as well as knowledge of Buruli ulcer in both the case and the control groups.

Data Analysis

The data obtained was analyzed using the Microsoft Excel of the computer. Descriptive summary statistics such as mean were derived and data was presented in tables. Odds ratio was calculated for the risk factor under evaluation. Association between the variable were calculated using appropriate statistical test and the level of significance set at $p \leq 0.05$.

RESULTS

A total of 120 subjects of 40 cases of Buruli ulcer and 80 controls were interviewed. The study population (cases) and control groups were very similar in terms of age ($P > 0.05$). Hence, the case and control groups were age-matched as shown in Table 1 above.

In Table 2 depicts the distribution of the subjects' educational levels, occupations, social history and comorbidities.

Table 3 shows the distribution of respondents according to other socio-demographic characteristics, i.e., sewage disposal method, sources of drinking water, type of living house, refuse disposal method, pet in the house, BCG vaccination, BCG scar present and visit to water body.

Table 4 depicts the distribution of the cases and control (where applicable) according to awareness,

characteristics and management of the ulcer among them. It shows that 5% and 1.25% of cases and control have heard about BU, just as the knowledge of risk factors in both groups was also poor. Lesion was found mainly in the lower limbs (70% of cases). Fifty per cent of cases applied no preventive measure while 40% of the control adopted the use of ITN as a preventive strategy. About 97% of BU victims applied wound dressing at a local patent medicine vendor's, while 95% of them took herbal concoctions before seeking help in hospital.

Table 5 shows that the male gender, poor education, visit to water bodies and absence of BCG vaccination are significantly associated with BU. However, farming, open dumping of refuse and poor sewage disposal are not significantly associated with BU.

DISCUSSION

This study analyzed some common risk factors associated with Buruli ulcer. The risk factors under analysis include gender, poor education, farming, poor sewage disposal, visit to water bodies, open dumping of refuse, no BCG vaccination, pet in the house, poor drinking water source and no preventive measure. Visit to water bodies is the leading associated risk factor was seen in 90% of cases. This agrees with a similar case-control study done in Ghana [7]. The increased risk for Buruli ulcer disease may have resulted from direct contact with contaminated water bodies and/or indirect exposure to riverine environment that harbor *Mycobacterium ulcerans*. The finding also supported previous investigations that noted an elevated risk for Buruli ulcer disease among Uganda tsetse flies control workers who frequented swampy areas [8] and among persons who farmed near the Lobo River in Cote D'ivoire [9]. This finding that regular visit to water bodies such as rivers, streams and ponds for activities like washing, swimming, fetching, irrigation as highest risk for Buruli ulcer concurred with study done in Suhum-Kraboia Coalter and Akuapem south districts of the eastern region of Ghana where presence of wet land, insect bites in water/mud, washing in the Densu river and house walls built with mud were identified as risk factors for Buruli ulcer disease [10].

The finding of males preponderance of Buruli ulcer disease and lesions on extremities agrees with findings of Pratima L et al in Ghana [7] but Ernest Kenu et al found almost equal preponderance between males 49.6% and females 50.4% [10]. The over representation of males suggests that some undiscovered common behaviour increases their risk for Buruli ulcer disease. The adventurousness of males and engagement in outdoor activities may account in part for this increased prevalence in males.

Farming was found not to be significantly associated with Buruli ulcer in this study. This is a surprise finding

Table 1: Age and sex distribution of the subjects

Age group (years)	Case			Control		
	Male	Female	Total	Male	Female	Total
<16	7	1	8	8	8	16
16-25	10	2	12	15	14	29
26-35	5	0	5	13	8	22
>35	6	9	15	5	8	13
Total	28	12	40	41	39	80
Mean age			16.40			16.21
SD			2.10			2.80
Z-test						0.447
p-value						p>0.05

Table 2: Distribution of subjects by other demographic characteristics

Variable	Cases	Control	Total	(X ² test) p-value (with BfC)*
Education of respondents				
No formal education	12	3		
Primary education	20	32		
Secondary education	8	21		p=0.001**
Tertiary education	0	24		
Total	40	80	120	
Occupation of respondents				
Student	18	35		
Farming	14	16		p=0.85
Civil servant/Teacher	6	19		
Trader/Driver	2	10		
Total	40	80	120	
Comorbidities				
Hypertension	6	9		
Tuberculosis/Diabetes	3	3		p=0.48
None	31	68		
Total	40	80	120	
Social history				
Smokes	1	3		
Drinks alcohol	15	27		p= 0.35
None significant	24	50		
Total	40	80	120	

*BfC – Bonferoni Correction; **statistically significant

Table 3: Distribution of respondents according to other socio-demographic characteristics

Variables	Cases	Control	(X ² test) Total p-value (with BfC)*
Sewage disposal method			
Pit toilet	24	40	p=0.7
Water closet	4	24	
Bucket	1	4	
Bush/open	11	12	
Total	40	80	
Sources of drinking water			
Stream/River/water body	31	12	p=0.01**
Pipe borne water	2	39	
Well	3	10	
Borehole	1	9	
Sachet/bottled water	3	10	
Total	40	80	120
Type of living house			
Public	19	14	p=0.001**
Private	21	66	
Total	40	80	
Refuse disposal method			
Open	28	53	p=0.1
Close	12	27	
Total	40	80	
Pet in the house			
Yes	18	15	p=0.015**
No	22	65	
Total	40	80	
BCG vaccination			
Yes	16	52	p=0.03**
No	24	28	
Total	40	80	
BCG Scar present			
Yes	14	51	p=0.6
No	2	1	
Total	16	52	
Visit to water body			
Yes	36	10	p=0.0001**
No	2	70	
Total	40	80	

*BfC – Bonferoni Correction; **Statistically significant

Table 4: Awareness, characteristics and management of the ulcer among the cases

Variables	Cases	% of total	Control	% of total
Heard about Buruli ulcer				
Yes	2	5%	1	1.25%
No	38	95%	79	98.75%
Total	40		80	
Knowledge of risk factors				
No idea	38	95%	78	97.50%
Acquired from the ground	2	5%	2	2.50%
Total	40		80	
Site of lesion				
Head	0	0%	NA	
Upper limb	12	30%	NA	
Trunk	0	0%	NA	
Lower limb	28	70%	NA	
Total	40			
Duration of lesion				
≤8 months	2	5%	NA	
>8 months	38	95%	NA	
Total	40			
Preventive measures adopted**				
None	20	50%	11	13.75%
Bathes after work	6	15%	27	33.75%
Bathes daily	5	12.5%	22	27.50%
Wears foot wear always	5	15%	15	18.75%
Wear protective clothing	4	10%	10	12.50%
Uses ITN	11	27%	32	40.00%
Treatment of ulcer before coming to hospital*				
Herbal concoctions	38	95%	NA	
Spiritual homes	30	75%	NA	
Wound dressing in local patent medicine store	39	97%	NA	

**Multiple responses for those who practice personal protection

*Multiple responses

NA – Not applicable

Table 5: Relationship between Buruli ulcer and the common risk factors

Buruli Ulcer Risk factors	Case	Control	Total OR	X ²	p-value
Gender (male)	28(70.0%)	41(51.3%)	69	3.84 =0.05*	2.22
Poor Education	32(80.0%)	35(43.8%)	67	14.27 =0.0003*	5.13
Farming	14(35.0%)	16(20.0%)	30	3.20 =0.07	2.15
Poor sewage disposal	12(30.0%)	16(20.0%)	28	1.49 =0.15	1.71
Visit to water bodies	36(90.0%)	10(12.5%)	46	67.78 =0.00000*	63
Open dumping of refuse	28(70.0%)	53(66.3%)	81	0.17 =0.83	1.19
No BCG vaccination	24(60.0%)	28(35.0%)	52	6.79 =0.01*	2.79
Pet in the house	18(45.0%)	15(18.8%)	33	9.25 =0.002*	3.55
Poor drinking water source	31(77.5%)	12(15.0%)	43	45.32 =0.00000*	19.52
No preventive measure	20(50.0%)	11(13.8%)			

*Statistically significant

when considered side by side with many studies which found Buruli ulcer more commonly among the rural farmers. This may be attributed to the fact that most people engaged in one form of farming activities or the other without regarding themselves as farmers. In most rural African towns, it is a common practice for young children to assist their parents in farming after school hours and/or on weekend without being labeled as farmers but students.

Poor water sources like rivers, streams and ponds were found to be significant risk factors of Buruli ulcer. This agrees with a study in Ghana assessed water related risk factors for Buruli ulcer [11]. This finding may not necessarily be related to use of water from rivers and streams for drinking, cooking, bathing and washing purposes but likely to be associated with activities such as swimming and playing in the rivers when fetching water. Persons who fetch boreholes and pipe-borne water are not likely to engage in these risk activities.

The study also found that BCG vaccination significantly reduces the risk for Buruli ulcer. Studies in Democratic Republic of Congo, Ghana and Togo reported similar findings in Ghana but contradictory results in DR Congo and Togo [12]. These discrepancies are explained by three main factors: the BCG strain used for vaccination, the population vaccinated and Mycobacterium disease. Although BCG vaccination appears to be effective against leprosy and may protect against Buruli ulcer disease within 1 year after vaccination, [13] the hypothesis that BCG vaccination provides lasting protection against Buruli ulcer disease is a matter for further research.

Keeping pets (domestic animals) in the house was found to be significantly associated with Buruli ulcer disease. There is no tangible explanation for this finding. It may be a co-incidental finding especially when it is known that Buruli ulcer is common among people with low socio-economic status. Persons of low socio-economic status are more likely to keep and live with domestic animals in their homes.

The study also found that non-practice of preventive measures significantly increases the risk for *Mycobacterium Ulceran* infections [14]. Bacteria contamination of skin surfaces may facilitate *Mycobacterium ulcerans* infection. The regular bathing may remove bacteria deposited on the skin. This study also corroborates the observation that wearing protective clothing is associated with decreased Buruli ulcer disease risk [9] and furnishes important clues about Buruli ulcer disease transmission. Taken together with the predominance of limbs lesions suggest that exposed skin facilitates infection. This study also confirms, however, finding of other studies that farming with long sleeves and long pants protect against Buruli ulcer [9, 15]. Long clothes may protect from small injuries or insect bites as possible means of entry for *Mycobacterium ulcerans*. The study also found that footwear use was significantly associated with lower odds of Buruli ulcer and it agrees

with findings of Sara Tomezy K. et al [16]. These findings are consistent with the mode of transmission of Buruli ulcer which includes presence of skin cut or abrasions and contact with water, soil or mud during work or recreational activities contaminated with human and animal excreta.

Poor education was found among Buruli ulcer patients, seen in 80% of cases. The finding is not surprising as Buruli ulcer is a disease associated with poverty, low socio-economic status and ignorance. A well educated person is more likely to have a high socio-economic status with high living standard which involves better source of drinking water, and good personal hygiene.

The study found a low level of awareness of Buruli ulcer disease and its risk factors among cases and control subjects. This agrees with similar study done in Ga West District of Ghana [17]. However, this was not in keeping with a similar study done in Southwest Cameroun which found that 84.4% of the studied population knew Buruli ulcer [6], but lack the knowledge of its aetiology and risk factors. The misconception found in this study attributing Buruli ulcer to witchcraft was similar to the above mentioned works and other studies of some African countries. Among the subjects who knew the cause and risk factors of Buruli ulcer, stratification with respect to level of education revealed a significant difference in their understanding of the cause of Buruli ulcer in the favour of well-educated people.

No community preventive measure/s were identified during the course of this research and personal hygiene practices found were mostly a part of general cleanliness and precautions not necessarily against Buruli ulcer.

Treatment seeking behaviour could be related to the perception of the cause of the disease. Majority believed that disease was caused by witchcraft and should be addressed by traditional healers or witchdoctors. All the patients interviewed have sought treatment from various traditional and herbal practitioners. Majority have visited various spiritual houses with no visible improvement or cure. This study found that ignorance and misconceptions were the major causes of delay in seeking appropriate treatment which led to severe form of the disease and complications, further supporting the need for intensive health education.

Limitations

Little research has been conducted on Buruli ulcer in the study area, with resultant paucity of literature on the subject matter.

CONCLUSION

This study has shown that a significant relationship exists between Buruli ulcer and the various risk factors as regular visit to water bodies, poor education, no BCG

vaccination and poor drinking water source. Exposure and/or contamination of skin may facilitate transmission, as suggested by the predominance of limb lesions and the protective effects of bathing and protective clothing. This study also clearly demonstrated that there is a wide gap in the public awareness for Buruli ulcer disease. Proper community education and mobilization are urgently needed to correct the misconception and improve the outcome of Buruli ulcer disease.

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Author Contributions

Adogu POU – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Guarantor of Submission

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Conflict of Interest

Authors declare no conflict of interest.

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