Individual Risk Factors of Mycetoma Occurrence in Eastern Sennar Locality, Sennar State, Sudan: A Case-Control Study

Rowa Hassan (Roaalbasha2016@outlook.com)
Mycetoma Research Centre, Soba University Hospital, University of Khartoum, Khartoum
Kebede Deribe
Children's Investment Fund Foundation, Addis Ababa
Hope Simpson
Department of Disease Control, London School of Hygiene and Tropical Medicine, London
Stephen Bremner
Department of Primary Care and Public Health, Brighton and Sussex Medical School, Brighton
Osama Elhadi Bakheet
Mycetoma Research Centre, Soba University Hospital, University of Khartoum, Khartoum
Mustafa Alnour
Department of Radiography, Faculty of Medicine, University of Khartoum , Khartoum
Ahmed Hassan Fahal
Mycetoma Research Centre, Soba University Hospital, University of Khartoum, Khartoum
Melanie Newport
Department of Global Health and Infection, Brighton and Sussex Medical School, Brighton
Sahar Bakhiet
Mycetoma Research Centre, Soba University Hospital, University of Khartoum, Khartoum

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Abstract

Mycetoma is a serious chronic subcutaneous granulomatous inflammatory disease that is endemic in tropical and subtropical regions where it impacts profoundly on patients, families, and communities. Individual-level risk factors for the disease are poorly understood. To address this, a case-control study was conducted based on data collected from 60 villages in Eastern Sennar Locality, Sennar State, Sudan.

Based on the presence of swelling in any part of the body, or sinus formation with or without grain discharge evident from the lesion by ultrasound examination, we diagnosed 359 cases of mycetoma. For each case, we included three healthy sex-matched persons, with no evidence of mycetoma, from the same village as the controls group (n=1077).

The odds for mycetoma were almost three times higher in individuals in the age group 16-30 years (Adjusted Odds Ratio (AOR) = 2.804, 95% CI= 1.424 – 5.523) compared to those in age group ≤15 years. Other factors odds of mycetoma were history of local trauma (AOR =1.892, 95% CI= 1.425 – 2.513), being unmarried (AOR =3.179, 95% CI= 2.339 – 4.20) and owning livestock (AOR =3.941, 95% CI= 2.874 – 5.405).

In conclusion, certain factors found to be associated with mycetoma in this study could inform a high index of suspicion for mycetoma diagnosis, which would improve early case detection. Other factors found to be associated could inform the development of an interventional program for mycetoma control in Sudan, including education on healthy farming practices and the risks of puncture wounds for individuals residing in endemic areas. However, this work was conducted in one endemic state, while mycetoma cases occur in all states of Sudan. Replicating this study over a wider area would give a fuller picture of the situation, providing the control program with more comprehensive information on the risk factors for the disease.

Introduction

Mycetoma is a devasting neglected tropical disease that occurs in tropical and subtropical regions [1]. It is characterized by painless subcutaneous masses with multiple sinuses draining seropurulent discharge and grain, most frequently affecting the feet and hands, though other parts of the body may be involved [2, 3]. The disease progresses to involve the skin, deep tissues, and bone, sometimes resulting in massive tissue destruction leading to significant deformities and disability [4]. The disease is associated with massive morbidity, stigma and reduced economic productivity [4, 5]. Mycetoma is reported worldwide and Sudan is considered the most endemic country, though mycetoma is commonly reported from Mexico, Venezuela, Mauritania, Senegal, Chad, Ethiopia, Somalia, Yemen, and India [6]. The geographical distribution of mycetoma depends on a range of environmental factors such as rainfall, humidity, and temperature [7]. A study conducted in Sudan indicated mycetoma is more likely to occur in arid areas proximal to water sources, soil with low calcium and sodium concentrations, and a variety of thorny tree species [8].

There is controversy on the route of infection in mycetoma; however, subcutaneous traumatic inoculation of the causative organism is the most favoured hypothesis based on current evidence [4].

The disease is most frequently reported in young adults aged 20-40 years, but people of all ages are at risk [9]. Males are reported to be at higher risk, but a community-based study in White Nile, Sudan, showed almost equal risk for both sexes [10, 11]. Mycetoma commonly affects those who work in close contact with the environment, such as farmers and shepherds [12]. Affected communities are generally of low socioeconomic status and underdeveloped infrastructure providing clean water and sanitation [13].

There are currently no dedicated control programmes for mycetoma, and the only available tools to reduce the disease burden are early case finding and appropriate management. These are hampered by challenges in the diagnosis and treatment of the disease and knowledge gaps surrounding its incidence, prevalence, and determinants of susceptibility [9–11]. Diagnosis requires numerous invasive and time-consuming investigations led by an experienced physician, and available treatment options are limited and expensive, require a long time to effect cure, and have a high recurrence rate [12, 13] [14, 15]. The promotion of early case detection is costly and relies on appropriate public health messaging and community education. Existing knowledge gaps surrounding the route of infection, factors favouring transmission, and determinants of susceptibility to the disease impede the design and implementation of effective prevention strategies [4, 16–18].

We sought to address this issue using a case-control study to determine risk factors for mycetoma infection in area highly endemic area of Sudan.

Methods

This population-based case-control study was conducted in Eastern Sennar Locality, Sennar State, central-eastern Sudan, and included 41,176 individuals. Eastern Sennar Locality is highly endemic according to surveillance databases from the Mycetoma Research Centre (MRC), a World Health Organization (WHO) Collaborating Centre on Mycetoma, and the reference centre for mycetoma management and research in Sudan.

The rationale for the is sample size is based on the assumption that the prevalence of mycetoma is five cases per 10,000 population, with the average population size of 935 people in the village, and the population of Eastern Sennar locality of 353,196 people. The calculations suggested that sampling 60 villages will give 80% power of detecting mycetoma at 5% significance level. Cases were identified through an exhaustive survey of 60/292 randomly selected villages in the five administrative units of the locality, described in more detail elsewhere [19]. The survey was conducted from June-July 2019, and every household in these sixty villages was visited. Cases were identified through clinical examination of all individuals by a medical doctor. When an individual was not at home at the examination, the household was revisited. All individuals with swelling of any part of the body or sinus formation, with or without grain discharge, were considered suspected cases of mycetoma. All suspected cases were referred to Wad Onsa Regional Mycetoma Centre, where an experienced radiologist performed lesion ultrasound examination to ascertain mycetoma diagnosis. A confirmed mycetoma case was defined as an individual with swelling or sinuses in any body part, with a pocket of fluid containing echogenic grains on ultrasound examination [20].

For each patient, three healthy controls were selected by simple random sampling. The control group was selected from households where no suspected case was detected and matched on community and sex.

After village leaders and the study population were informed about the survey objectives and process, all households in the study villages were visited. The questionnaire was written in English and was validated by a team including a medical doctor and a statistician at the MRC. Responses were captured through electronic data capture forms through open-source software called Open Data Kit (ODK), which collects, manages, and uses data in resource-constrained environments, running via Android devices. It allows for offline data collection with mobile devices in remote areas.

Household-level data included the type of material of the floor, roof, external walls of the dwelling, and hygiene and sanitation amenities. Individual-level factors included age, sex, marital status, educational level, occupation, swelling, history of trauma and wearing shoes/slippers at home and work. Further details, including clinical features, lesion onset, duration, site, and mycetoma family history, were collected from suspected cases.

Data were sent directly to a server at the MRC and imported to the Statistical Package for Social Sciences, SPSS 25 (SPSS, Chicago, IL, USA) for analysis. Descriptive analysis was performed, and bivariate analysis (chi-square test) was used to identify any statistically significant associations between explanatory variables and the outcome variable (confirmed mycetoma).

Univariate and multivariate analyses were undertaken to assess the strength of association of individual and household-level variables with disease status (i.e., being a mycetoma case or control). A stepwise forward and backward selection procedure was used to select inclusion variables in a conditional logistic regression model. P-value of 0.05 or less was used to enter variables into the model and 0.1 or above for removal from the model The strength of association of each retained variable with mycetoma was expressed using adjusted odds ratios with their 95% confidence interval (CI).The STROBE case-control reporting guidelines were used in this study [21].

Results

Demographic characteristics of cases and controls

A total of 1,436 individuals (359 mycetoma patients and 1,077 controls) were included in the study. The mean age of confirmed mycetoma patients was 27.0 (SD=16.3) years, ranging from 1- 85 years. The mean age of controls was 37.2 (SD=16.9) years, ranging from 1-105.

The patient group comprised 174 males (48.5%) and 185 females (51.5%), and the control group 537 (49.9%) males and 540 (51.1%) females. Sixty-seven (18.7%) cases and 236 (21.9%) of controls worked as shepherds or farmers. One hundred and thirty-nine cases (38.7%) and 525 controls (48.7%) were illiterate.

Clinical Characteristics Of Cases

In total, 290 cases (80.8%) presented with visible swelling, and 241 (67.1%) had lesions in the lower extremities. Sinuses were present in 138 (38.4%), and of those, 122 (33.9%) patients had discharge. One hundred and twenty-nine cases (35.9%) had a history of local trauma at the mycetoma site.

Age, history of trauma, marital status, education, raising animals within the household and livestock ownership were strongly associated with the odds of mycetoma (p-value <0.05). Compared to individuals aged 0- 15, the odds of mycetoma were more than six times higher in individuals in the age group 16-30 years (OR = 6.467, 95% CI= 3.421 - 12.224, $p < 0.001$), and around two times higher those aged 31-45 or 46-60 years. The likelihood of mycetoma in individuals with a history of trauma was 71% higher than in those without (OR = 1.710, 95% CI= 1.323 - 2.209, $p < 0.001$). The odds of mycetoma in unmarried individuals were over four times that in married individuals (OR = 4.117, 95% CI= 3.151 - 5.381, $p < 0.001$), while illiterate individuals lower odds (OR = 0.664, 95% CI= 0.521– 0.848, $p = 0.001$). Compared to individuals in other occupations, housewives had increased odds of mycetoma (OR = 4.945, 95% CI= 2.747 – 8.902, $p < 0.001$), as did those who were desk employees (odds ratio, 1.251, 95% CI= 1.279 – 3.961, $p = 0.005$). Individuals living in households with animals raised within the dwelling had lower odds (OR = 0.557, 95% CI= 0.435 – 0.713, $p < 0.001$). Ownership of animals increased the odds of mycetoma by more than two times (OR= 2.15, 95% CI= 1.687 – 2.742, $p < 0.001$). (Table 1)

Table 1
Demographic characteristics of confirmed cases and controls, showing unadjusted odds ratios (OR) for mycetoma risk factors (n=1436)

Characteristic	Cases No. (%)	Controls No. (%)	Crude OR (95%CI)	*p*-value
Individual factors				
Age group				
0-15 Years	70 (19.5%)	70 (6.5%)	1.0	
16-30 Years	136 (37.9%)	391 (36.3%)	6.467(3.421 - 12.224)	<0.001
31-45 years	101 (28.1%)	344 (31.9%)	2.249 (1.262 - 4.008)	0.006
46-60 Years	37 (10.3%)	175 (16.2%)	1.899(1.055 - 3.416)	0.032
>60 Years	15 (4.2%)	97 (9.0%)	1.367(0.714 - 2.617)	0.345
Sex				
Female	185 (51.5%)	540 (50.1%)	1.0	
Male	174 (48.5%)	537 (49.9%)	1.069(1.414 - 2.290)	0.583
Trauma history				
Yes	129 (35.9%)	266 (24.7%)	1.710 (1.323 – 2.209)	<0.001
No	230 (64.1%)	811 (75.3%)	1.0	
Marital status				
Married	207 (57.7%)	905 (84.0%)	1.0	
Unmarried	152 (42.3%)	172 (16.0%)	3.864(2.963 – 5.038)	<0.001
Education level				
Literate	220 (61.3%)	552 (51.3%)	1.0	
Illiterate	139(38.7%)	525 (48.7)	0.664 (0.521– 0.848)	0.001
Wear shoes/ Slippers				
Both work and home	261 (72.7%)	828 (76.9%)	1.0	

Characteristic	Cases No. (%)	Controls No. (%)	Crude OR (95%CI)	*p*-value
At work or at home only	32 (9.8%)	84(7.8%)	0.788 (0.574 - 1.083)	0.142
Not at all	66 (18.4%)	165 (15.3%)	0.952 (0.579 - 1.566)	0.847
Occupation				
Farmers or shepherds	67 (18.7%)	236 (21. 9%)	1.0	
Students	67 (18.7%)	60 (5.6%)	1.257 (0.728 – 2.170)	0.411
Housewives	114 (31.5%)	447 (41.5%)	4.945 (2.747 – 8.902)	<0.001
Merchants	15 (4.2%)	76 (7.1%)	1.129 (0.674 – 1.893)	0.644
Unemployed and underage of work	61 (17.3%)	120 (11.1%)	0.874 (0.422 – 1.811)	0.717
Desk employee	5 (1.4%)	29 (2.7%)	1.251 (1.279 – 3.961)	0.005
Freelancer	21 (5.8%)	93 (8.6%)	2.491 (0.969 – 6.403)	0.058
Other jobs	9 (2.4%)	16 (1.5%)	0.764 (0.264 – 2.205)	0.618
Household factors				
Source of fuel for cooking				
Wood and Animal dung	243 (67.7%)	433(40.2%)	0.600 (0.429 – 0.839)	0.003
Gas and Coal	77 (21.4%)	130 (12.1%)	1.0	
Any source of fuel available	35 (9.7%)	500 (46.4%)	0.403 (0.286 – 0.569)	<0.001
No food cooked in the house	4 (1.1%)	14 (1.3%)	0.476 (0.151 – 1.498)	0.205
Main material of dwelling floor				
Brick/cement/ceramic	20(5.6%)	50 (4.6%)	2.160 (1.372 - 3.400)	0.001

Characteristic	Cases No. (%)	Controls No. (%)	Crude OR (95%CI)	*p*-value
Earth/soil and/or sand	326 (90.8%)	1007 (93.5%)	1.0	
Combination	13 (3.6%)	20(1.9%)	1.271 (0.554 – 2.913)	0.571
Main material of dwelling roof				
Traditional/wood/zinc/plastic cover	256(71.3%)	760 (70.6%)	1.101 (0.764 – 1.588)	0.605
Concrete	42(11.7%)	145(13.5%)	1.0	
Combination	61 (17.0%)	172 (16.0%)	1.169 (0.748 – 1.826)	0.493
Main material of dwelling exterior walls				
Wood	40 (11.1%)	104 (9.7%)	0.824 (0.525 – 1.294)	0.401
Mud and/or animal dung	114(31.8%)	371 (34.4%)	0.847 (0.626 – 1.147)	0.284
Red bricks and/or concrete	97 (27.0%)	324 (30.1%)	0.786 (0.572 – 1.079)	0.137
No walls	108 (30.1%)	278 (25.8%)	1.0	
Animal raised within the dwelling				
Yes	127 (35.4%)	534 (49.6%)	0.557 (0.435 – 0.713)	<0.001
No	232 (64.6%)	543 (50.4%)	1.0	
Livestock ownership				
Yes	183 (51.0%)	351 (32.6%)	2.151 (1.687 – 2.742)	<0.001
No	176 (49.0%)	726 (60.4%)	1.0	
OR= Odds Ratio, CI= Confidence Interval				

Multivariate Analysis

After adjusting for other significant variables, being unmarried had higher odds of mycetoma (AOR = 3.179, 95% CI= 2.339 – 4.20, p <0.001). The odds of the disease were roughly double for patients with a history of local trauma compared to those without (AOR = 1.892, 95% CI= 1.425 – 2.513, p <0.001).

Those aged 16-30 had higher odds (AOR = 2.804, 95% CI = 1.424 – 5.523, p =0.003) compared to those aged ≤15 years. Illiterate individuals had lower odds of mycetoma (AOR = 0.685, 95% CI= 0.521 – 0.900, p= 0.007). Individuals who owned animals had higher odds of mycetoma (AOR = 3.914 ,95% CI= 2.874 – 5.405, p< 0.001), but those keeping animals within their own dwelling had lower odds of disease (AOR = 0.310, 95% CI= (0.303, 95% CI= 0.220 – 0.416, p< 0.001) (Table 2).

Table 2
Individual risk factors for mycetoma at Eastern Sennar locality, Sennar State (n=1436)

Individual Characteristics	Cases No. (%)	Controls (%)	AOR (95%CI)	p-value
Age group				
0-15 years	70 (19.5%)	70 (6.5%)	1.0	
16-30 years	136 (37.9%)	391 (36.3%)	2.804 (1.424 – 5.523)	0.003
31-45 years	101 (28.1%)	344 (31.9%)	1.564 (0.852 – 2.871)	0.149
46-60 years	37 (10.3%)	175 (16.2%)	1.469 (0.791 – 2.726)	0.223
> 60 years	15 (4.2%)	97 (9.0%)	1.218 (0.617 – 2.405)	0.570
Trauma history				
Yes	129 (35.9%)	266 (24.7%)	1.892 (1.425 – 2.513)	<0.001
No	230 (64.1%)	811 (75.3%)	1.0	
Marital status				
Married	207 (57.7%)	914 (84.9%)	1.0	
Unmarried	152 (42.3%)	163 (15.1%)	3.179 (2.339 – 4.20)	<0.001
Education level				
Literate	220 (61.3%)	559 (51.9%)	1.0	
Illiterate	139 (38.7%)	518 (48.1)	0.685 (0.521 – 0.900)	0.007
Animal raised within the dwelling				
Yes	127 (35.4%)	534 (49.6%)	0.303 (0.220 – 0.416)	<0.001
No	232 (64.6%)	543 (50.4%)	1.0	
Livestock ownership				
Yes	183 (51.0%)	351 (32.6%)	3.941 (2.874 – 5.405)	<0.001
No	176 (49.0%)	726 (60.4%)	1.0	
AOR= Adjusted Odds Ratio, CI= Confidence Interval				

Discussion

Although mycetoma is a serious disease, inflicting disability and stigma on patients across many parts of the world, there remain essential questions about its epidemiology, particularly the risk factors for the disease. In the current study, patients with confirmed mycetoma were compared to the community- and sex-matched controls to identify determinants of risk in the study population. To the best of our knowledge, this is the first population-based case-control study of sociodemographic risk factors for mycetoma, providing evidence likely to apply to other settings and support global control efforts.

One of the risk factors we identified was a history of trauma, which roughly doubled the odds of mycetoma. This finding represents the most substantial epidemiological evidence for the theory that skin trauma may facilitate the inoculation of mycetoma-causative organisms into the subcutaneous tissue- although this does not rule out other possible routes of transmission [22]. This hypothesis is supported by the fact that mycetoma-causative organisms typically reside in the soil and evidence that certain *Acacia* trees- whose thorns may facilitate inoculation- are associated with environmental suitability for the disease [8]. However, previous analyses of mycetoma cases have shown a history of trauma in only a few patients, hypothesized to reflect that the trauma may be minor and pass unnoticed by the patient [9]. The case-control design we employed, including many patients and community-matched controls, allowed us to demonstrate a significant difference in the history of trauma between these two groups.

Many reports in the literature show that young adults and children are the most affected populations [2, 6, 23, 24]. The data obtained in this study showed that the, most common age group affected is the category 16-30 years. This higher odds in younger adult groups is likely to reflect that these individuals are more likely to be actively engaged in activities such as agricultural work and animal grazing, which expose them to mycetoma-causative agents in endemic areas.

As expected, livestock ownership was a strong risk factor for mycetoma. There are several possible mechanisms by which people who raise animals may be at increased risk of mycetoma. People living in rural areas tend to make animal enclosures from the wood of thorny trees and may be at risk of thorn pricks during the construction and maintenance of these structures [9]. As well as being in close contact with the environment, they are likely to be at higher risk of ticks, which are highly prevalent in domestic animals in Eastern Sennar Locality and hypothesized to play a role in the transmission of mycetoma causative agents to humans [25]. The evidence for this route of transmission is not conclusive, however. While the DNA of mycetoma-causative organisms has been isolated from ticks, this does not prove they are involved in transmission.

We found that the odds of unmarried individuals to contract mycetoma is four times compared to married counterparts. This is likely to reflect the social stigma of mycetoma, which may mean affected individuals are less likely to get married, or more likely to get divorced if they contract the disease after marriage. In rural communities, early marriage is often considered mandatory and social pressure is put on young adults to get married by early teen years. If they fail to get married early, this pressure can cause phycological distress in addition to the stress and depression occurring as a result of such a stigmatizing disease [26].

Interestingly, there was no significant difference between literate and illiterate populations and increased odds for mycetoma in desk employees, contradicting previous reports in the literature that mycetoma is commonly prevalent among poor communities with low education levels [4]. This may be explained by the fact that in mycetoma-endemic areas, most individuals share the same social and economic activities and behaviour irrespective of their educational level due to economic constraints. Another factor may be that schools in rural areas are limited to certain areas, and students often have to walk for long distances, putting them at higher risk of contact with mycetoma-causative organisms. We also observed that housewives and desk employees had increased odds of mycetoma; usually, housewives are responsible for the cooking, and hence they walk long distances to collect wood to use as fuel. Furthermore, housewives work in farming, especially in harvesting season, which may mean that they have a similar level of exposure.

Conclusion

In this population-based case-control study on mycetoma, the first of its kind at this scale, the high number of participants enabled precise estimates for the strength of association of various risk factors with disease. The methods used for confirmation of the disease, including clinical examination of all individuals, followed by ultrasound examination for confirmation, also meant that cases and controls were classified with high accuracy. One limitation of this study was that some suspect cases were lost to follow-up and were not included in the comparative analysis. However, we have no reason to believe that the absence of these individuals was due to their disease status or other systematic factors, so consider this data to be missing at random.

The results of this study could be applied to inform the future control of mycetoma. Efforts to raise awareness among clinicians of mycetoma risk factors- particularly age, history of trauma, and ownership of animals- could promote earlier diagnosis and treatment of mycetoma in patients presenting swellings or wounds in endemic regions of Sudan. These factors could also inform the design of health awareness campaigns in communities at risk, educate the population about activities that may put them at risk of the disease and encourage them to present early to health facilities if they experience early signs. Finally, this study adds further evidence for the substantial social impact of the disease and the stigma associated with it, which should not be overlooked in assessments of its global burden.

Abbreviations

AOR
Adjusted Odds Ratio
BSMS
Brighton and Sussex Medical School
CI
Confidence Interval
DNA
Deoxyribonucleic Acid
IRB

Institutional Review Board

MRC

Mycetoma Research Centre

ODK

Open Data Kit

OR

Odds Ratio

SPSS

Statistical Package for Social Sciences

WHO

World Health Organization

Declarations

Ethics approval and consent to participate

The research have been conducted in accordance to the declaration of Helsinki and ethics approval was obtained from the Mycetoma Research Centre, Institutional Review Board (IRB) Khartoum, Sudan (approval no. SUH 11/12/2018) and from the Brighton and Sussex Medical School (BSMS) Research Governance and Ethics Committee (ER/BSMS435/1). Written informed consent was obtained from each adult patient, and parents or guardians of the population under the age of 18 years.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to maintain patients' privacy but are available from the corresponding author on reasonable request on the following email:

Competing interests

The authors declare that they have no conflicts of interest

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Authors' contributions

All authors contributed to the manuscript and have read and approved the final version. RH led fieldwork and data collection. OEB, MA were responsible for the Ultrasound diagnosis. RH and KD were responsible for data analysis and data validation. RH, KD, HS, SB, AF, MN and SB were responsible for writing the manuscript and revision.

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Corresponding author

Correspondence to Rowa Hassan

Consent for publication

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