MYCETOMA Research Center
University of Khartoum
WHO Collaborating Center on Mycetoma

Report on
The Mycetoma Research Gaps Seminar

Thursday, 13th July 2017

9:00am- 3:00pm

Ministry of Higher Education & Scientific Research

Session 1 Summary:

Prof Fahal: Mycetoma, A Neglected Tropical Disease

- The objective of the session was to share the current status of mycetoma, to discuss mycetoma as a socio-economic dilemma affecting a large group of patients in Sudan and globally.
- There is a massive gap in the epidemiology, diagnosis, pathogenesis and management.
- The incidence and prevalence are not well studied.
- The organism was not isolated from the soil of endemic areas but a trace of its DNA was found. **This poses certain questions:**
    1. Is there an intermediate host for mycetoma?
    2. What is happening in the environment?
    3. Why not all people are infected?
    4. What is the role of the thorn?
    5. How do patients develop the infection? Is it environmental, is it genetic or immunogenic?

- School Students represent 30% of the patients affected leading to huge disabilities and drop out of school.
- Pregnant ladies have aggressive disease due to the physiological decrement in their immune response.
- The same patient may have multiple lesions that could be from the same or different causative organisms.
- Diagnosis is expensive and invasive. There is no point of care testing where mycetoma is endemic. Current tests have low sensitivity and specificity.
- The current management is not good enough. This could be due to low socioeconomic status which makes treatment unaffordable, poor health education and resorting to local and traditional medical treatment.

- **The challenges are:**
    1. Low cure rate
    2. High recurrence rate
    3. High patients drop-out
    4. The grains isolated from treated patients grow viable fungi when cultured. Therefore, **these drugs only limit the extent of the infection rather than fully cure the disease.**
    5. There are currently no drugs on the pipeline.

1. **Urgent needs:**
    1. Effective drugs
    2. Point of care diagnostics
    3. Good prevention plan

Session 2 Summary

Prof Ahmed Mudawi Musa: Immunology of Mycetoma

- There are limited studies that address the immunology of Mycetoma, due to the lack of funding and global attention.
- There is strong role of the neutrophils in the immune response.
- Which one of the TLR is specific to the immune response against mycetoma?
- It was discovered that **IgG subclass 1** in granulomatous tropical diseases is a recovery marker and therefore can be used to follow up patients' progress.
- The role of **T regulatory cells** should be investigated.
- IL-1B cytokine plays an important role in the reduction of infection propagation. It can stop the disease or reduce its progress.
- Only few in-vitro studies about the immune response of mycetoma are available. There is a need for more studies in humans.
- Persistent infection suppresses antigen presentation and therefore leads to inappropriate immune response.

Humoral immune response is a hot area for research.

1. Is it possible to make use of antibodies production in endemic areas?
2. What is the cut-off value of antibodies to differentiate between exposure and infection?
3. There is variability in immune response. There are severely ill patients that do not produce antibodies (false negative)
4. It can be used to assess the epidemiology of the disease (exposure, subclinical infection, infection and remission)
5. How long do antibodies remain in the blood
6. Cross reactivity of the immune response and antibodies to the different species that cause mycetoma.

Cell-Mediated Immunity:

Th1 is responsible for the curative immune response while Th2 is related to the pathogenesis. Mixed type of immune response is the cause of chronicity.

The Way Forward:

1. Natural history of infection (specially incubation period)
2. Prevalence of the disease
3. Follow up of patients after treatment
4. Developing diagnostic tests
5. Immunochemotherapy
6. Vaccinations and immune stimulation

Session 3 Summary

Dr. Sahar Bakhiet: Diagnostic Gaps in Mycetoma

Available diagnostic techniques have many drawbacks:

- Imaging requires high expertise to differentiate between mycetoma and other diseases that affect the bone and soft tissue.
- Examination of the grains is not definitive due to the overlapping morphological features of grains formed by mycetoma causative organisms.
- Culture is the gold standard diagnosis technique; however it is time consuming and associated with high risk of contamination.
- Histology is not definitive for species and requires confirmation.
- Serology is tedious, antigens are crude and not standardized. Sometimes it is negative especially in early cases.
- Molecular methods are too expensive, require equipment not available at point of care, and are time consuming.

The recent technique LAMP results can be seen visually with fluorescence and can be adopted for Mycetoma.

There is a need for a Rapid diagnostic test (RDT) that can be used at the point of care, with the following characteristics;

1. High quality
2. Easy to use
3. Based on agglutination, immune dot or ICT.
4. Quick same day results.
5. Cost effective.

Ongoing Research

RDT for mycetoma diagnosis: to identify antigens using proteomics, genomics and immune-analysis.

- Molecular tools need to be optimized for early case detection.

Session 4 Summary

Prof Sami Khalid: Treatment gaps

- No antifungal has been developed since 2000 and very few are in the pipeline.
- Large companies do not invest in finding new compounds.
- Similarities between humans and fungi lead to drug toxicity.
- Agrichemicals (pesticides) have azole chemical nature leading to resistance of naïve patients to azoles.
- Drug development pipelines are expensive due to the need of target identification, development of screening assays, finding leads, animal assays, and assessment of drugs effectiveness.
- Knowing the aetiological gaps is important for proper treatment.
- Mycetoma causative organisms might be endophytes or might be found in animal dunks.
- The lack of correlation between the in-vitro susceptibility and the clinical response to antimycetomal drugs could be attributed to:
    1. The drugs Pharmacokinetics
    2. Melanin
    3. Resistance due to azole based agrichemicals.

Strategies that can be used to bridge the treatment gaps:

1. Modification and combination of current antifungals
2. Repurposing of marketed drugs
3. Using natural compounds as a source of new leads.

Session 5 Summary

Prof. Muntasir and Dr. Mohamed Omer:

Exome sequencing and personalized medicine

- Exome sequencing of mycetoma patients is important for determining:
    1. Genetic predisposition
    2. Gene interaction during the disease

3. Designing customized personalized treatment

- The exome sequencing project of mycetoma patients is aimed at finding genetic variants and determining their importance and priority in disease susceptibility

Session 6 Summary

Prof. Mutamad Amin: Disease control and prevention gaps

- Due to the lack of knowledge of mycetoma life cycle, it is difficult to group it into a specific disease category. Thus, this makes it difficult to produce a proper control program.
- Landscape (spatial) epidemiology is needed to map risks. Geographical Information System, areas of high risk should be mapped.

- **The question is: what are the criteria of a high risk area?? Incidence? Prevalence? Environmental factors?**

Session 7 Summary

Dr. Musab Siddig: Advocacy Gaps

- The advocacy efforts of Mycetoma and its classification as an NTD collaterally helped the WHO to include other diseases on the list such as scabies.
- There are 5 main advocacy efforts in Mycetoma. The most important parts are to push mycetoma high up and highlight its importance, and to improve public awareness about the disease.
- **How can we address the gaps in advocacy?**
    1. KAP studies to identify issues and analyze problems.
    2. Evaluate the capacity to implement and assess the willingness of policymakers to support.
    3. Address human rights and SDGs.
    4. Assessment of current interventions.
    5. M&E

Session 8 summary

Social Science Students: Mycetoma Social Impact

- The locals classify the stages of the disease to Nabit, Madura, and Mycetoma in order of increasing severity.
- The religious and educational prospective of the community affect the way how they perceive the disease: Religiously conservative communities with low educational levels believe that mycetoma is caused by lack of religious commitment or due to the acts of sorcery. These types of patients usually resort to traditional and religious treatments. On the other hand, more educated communities believe

that there is an environmental cause for the disease and hence they usually seek medical treatment. There are also communities that have a mixed view about the cause of the disease.

- There is a high incidence of mycetoma in villages with homogenous ethnicities and social groups while incidence decrease with heterogeneity. This raises the question of whether genetic factors might be involved in the disease.

The positive effect of the disease on the community was the increased social connections and support between affected patients and their families. However on the negative side, mycetoma represents a social stigma for affected communities and particularly females. Mycetoma patients are often regarded as sinners and criminals.

Providing free medical treatment greatly alleviated the negative economic impact on affected patients. However since this support is not provided by the government, patients are concerned about its sustainability.

There are no psychological support facilities in all mycetoma treatment centers that could help patients to deal with the disease.

The locations of mycetoma treatment centers in Khartoum and Wad Onsa are relatively far from affected communities. Furthermore, the presence of the center in Wad Onsa presented a social stigma for the local community since the village is not highly endemic with the diseases. On the other hand villages with higher prevalence of mycetoma think that the center should have been built in their villages. Moreover, some patients withstand treatment at these centers because they think that they are for political advocacy and hence treatment in those centers means the support of certain political views.

Recommendations:

- Improving the training of currently available treatment teams.
- Integrating psychological aspects in treatment of patients.
- Appointing staff members that have no political affiliations that might affect patient's acceptance for treatment.
- Appointing social sciences experts at the mycetoma treatment centers.
- Appointing staff members that have no political affiliations that might affect patient's acceptance for treatment.
- Increasing mycetoma health education in affected villages.

Session 9 Summary

Prof. Ahmed Fahal: Mycetoma funding opportunities

The most important step for finding research funds is to write proper proposals and knowing how, when and where to present them.

There are three main research funding bodies:

1. Organisations such as; GHIT, NHR, HORIZON 2020, Welcome trust, Bill and Melinda Gates foundation, EDCTP, WHO/TDR, Embassies, and the ministry of higher education.
2. Collaborative centre such as; CDC. Erasmus medical center, CBS, Newcastle University, and SBWTGHC.
3. Sponsors such as the DNDi

Discussions, Questions, Comments, and Recommendations

- Screening plants found in endemic areas for potential new drugs?
- Screening Moringa, Neem, and camels' milk and urine for potential new drugs?
- Are there available antigens identified? We need to work on the characterization of antigens.
- Studying other neglected fungal diseases in Sudan such as Aspergillosis.
- Creating multi-disciplinary teams for field visits that include veterinarians, anthropologists and various other specialties.
- Importance of mentoring: Founding a mentorship programme of expertise in various disciplines that would help young researchers with their proposals before applying to grants.
- Investigating the reasons behind the solo survival of *Madurella mycetomatis* inside the open lesions of affected patients which could be radially contaminated with viruses, bacteria and other pathogens.
- The current project that is aimed at sequencing four strains of *M. mycetomatis* will aid in finding novel antigens and proteins that can be used in the diagnosis and treatment of the diseases.
- There is a hypothesis that the adjuvant use NSAIDs can improve the treatment of Mycetoma.
- What is the definition of a high risk area? Is it the clustering of endogenous cases or other environmental parameters?
- Investigating the impact of poor nutrition of the disease outcomes. What could be an immune potentiator? Researching the effect of nutrition on disease outcome.
- Mass spectrometry could be a good potential tool for rapid diagnosis of Mycetoma causative organisms.
- Designing new formulation for existing antifungal drugs could be used for site directed therapy.
- Using the small differences between the human and fungal genome in finding potential selective drugs targets.
- Identification of proteins and antigens may be an area to explore to create vaccines.
- Could there be a role of a urinary antigen test for mycetoma to be used for diagnosis (at point of care), similar to the experience of Leishmaniasis?
- Measurement of the immunoglobulins subclasses is needed.