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Mycetoma: an old and still neglected tropical disease

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Mycetoma is a chronic infection caused by either fungi or filamentous bacteria that are known as eumycetoma or actinomycetoma, respectively. It is characterised by massive deformity and severe disability. Although described from antiquity in Indian writings, it was first described in the western literature by the naturalist, historian and physician, Englebert Kaempfer, who, while his ship had moored off the coast of Southern India, travelled through the local area describing a variety of unusual illnesses, one of which was mycetoma. While seldom common, it is a continuing source of consultation by patients in many tropical regions of the world from Mexico to Thailand.[1] But the largest numbers of cases have been reported from Mexico, Sudan and India. Despite the increasing interest of a small group of active investigators and clinicians, mycetoma has remained a disease that is generally inaccurately diagnosed and poorly managed except in a few centres where special interest has led medical teams to make a closer study of this infection. In 2013, it was listed by WHO as a neglected disease.[2]

There remain a large number of mysteries surrounding this condition. The causative organisms can be found in the environment in soil or plant material such as *Acacia* thorns. Penetrating injury was always assumed to be the prelude to infection. However, it has recently become clear that distribution is by no means uniform, and even in endemic areas there are hyperendemic communities where the prevalence rate can exceed 10% of the population.[3] Equally there may be a small shift in the pattern of organisms within the same country. For instance, in Mexico in the state of Monterrey the cause of infection is overwhelmingly the actinomycete, *Nocardia*, whereas in parts of the Costa Chica, Guerrero state, fungi dominate as the causative organisms.[4] Attention has therefore focused on possible co-factors involved in the pathogenesis disease. These include the presence of cattle and cattle dung in areas of high endemicity and the finding that there is a population prevalence of mutations found by single nucleotide polymorphisms in patients with mycetoma from endemic areas in Sudan, in genes encoding CC chemokine ligand 5 and interleukin-10 promoter regions.[5] These suggest underlying susceptibility involving macrophage recruitment and function may play a role in determining the outcome of an initial injury and implantation of potentially causal organisms.

Once the organisms invade, they assume a new growth pattern characteristic of mycetoma, forming micro-colonies called grains in subcutaneous tissues. The morphology of the organisms in these structures alters dramatically with both cell wall thickening and replication as well as unfolding of the carbohydrate cytoskeleton that allows binding of adjacent cells.[6] In the case of eumycetomas, confirmation of the clinical diagnosis is frequently hampered by the slow growth of the organisms in culture and, often, the lack of identifying features such as conidia (spores). But the advent of molecular diagnostic methods has begun to change the situation with a reclassification of the organisms and recognition that many more fungi can cause this disease. Whereas previously there were only two *Madurella* species implicated in mycetoma, *M. mycetomatis* and *M. grisea*, three more *Madurella* species have been added, *M. pseudomycetomatis*, *M. fahalii* and *M. tropicana*,[7] and speciation appears to have implications for both epidemiology and drug sensitivity. Imaging investigations have also advanced with magnetic resonance imaging playing an increasingly important role in disease assessment,[8] but cheaper alternatives such as ultrasound are also being used with effect to define the extent of the infection.

Treatment remains a major cause for concern. In *Nocardia* actinomycetomas there is increasing interest in using agents other than cotrimoxazole and rifampicin, a former staple approach to treatment, with newer antibacterials such as amikacin, moxifloxacin and imipenem being found to have greater efficacy.[9] For the fungal mycetomas, though, the antifungal choice is limited with older drugs such as itraconazole being widely used. Another azole antifungal, ketoconazole, has some efficacy in mycetoma but its recent removal from the market in Europe, where it was used for superficial mycoses, may have an adverse effect of drug availability for deep infections in other parts of the world. There is limited evidence that newer azoles such as voriconazole may be more active, largely through the fact that they

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lack the melanin binding properties of other drugs; as a consequence voriconazole is more bioavailable per unit dose.[10] However, cost remains a potent bar to the use of the newer antifungals in resource-poor countries. In addition, uncertainty surrounding the continued development of other antifungals that may appear promising in vitro, such as ravuconazole, does not provide a healthy prospect for the availability of new therapies in the near future. Finally, there are currently neither preventive control measurements nor any vaccine for mycetoma due to the current state of knowledge of its route/source of infection, susceptibility and resistance.

What are the needs for mycetoma? The list is long,[11] although international recognition, long in coming, may add an incentive to further work. Our understanding of the global distribution of mycetoma is patchy although recent efforts to improve this situation may well bear fruit.[1] However, top clinical priorities are the introduction of systems that allow early recognition of new cases at rural health-post level; early institution of treatment may well provide a more successful answer to management.[12] This needs to be coupled with increased availability of effective medications subject to cost. The burden of this disease falls on a relatively small number of patients in the poorest of countries, which makes the delivery of therapies for mycetoma a potentially achievable target for focused donor programmes. Engagement with the pharmaceutical industry and international bodies such as WHO may create the necessary structure to implement this type of action. This needs to be coupled with two other initiatives. Understanding the pathogenesis of mycetoma could potentially provide the basis for new treatments or treatment combinations. Assessing the burden of mycetoma as a global disease is also a key element of this plan. At present, the Global Burden of Disease study[13] does not include this infection as a separate entity and yet data arising from such work would provide further impetus to control and possibly eliminate this troublesome infection.

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References

1 van de Sande WW. Global burden of human mycetoma: a systematic review and meta-analysis. PLoS Negl Trop Dis 2013;7:e2550.

2 WHO. Neglected Tropical Diseases: mycetoma. Geneva: World Health Organization; 2014. http://www.who.int/neglected_diseases/diseases/mycetoma/en/ [accessed 10 December 2014].

3 Samy AM, van de Sande WW, Fahal AH, Peterson AT. Mapping the potential risk of mycetoma infection in Sudan and South Sudan using ecological niche modeling. PLoS Negl Trop Dis 2014;8:e3250.

4 Bonifaz A, Tirado-Sánchez A, Calderón L et al. Mycetoma: experience of 482 cases in a single center in Mexico. PLoS Negl Trop Dis 2014;8:e3102.

5 Mahmoud NA, Fahal AH, van de Sande WW. The association between the interleukin-10 cytokine and CC chemokine ligand 5 polymorphisms and mycetoma granuloma formation. Med Mycol 2013;5:527–33.

6 Wethered DB, Markey MA, Hay RJ et al. Ultrastructural and immunogenic changes in the formation of mycetoma grains. J Med Vet Mycol 1987;25:39–46.

7 De Hoog GS, van Diepeningen AD, Mahgoub El S, van de Sande WW. New species of Madurella, causative agents of black-grain mycetoma. J Clin Microbiol 2012;50:988–94.

8 El Shamy ME, Fahal AH, Shakir MY, Homeida MM. New MRI grading system for the diagnosis and management of mycetoma. Trans R Soc Trop Med Hyg 2012;106:738–42.

9 Welsh O, Al-Abdely HM, Salinas-Carmona MC, Fahal AH. Mycetoma medical therapy. PLoS Negl Trop Dis 2014;8:e3218.

10 Van de Sande WW, de Kat J, Coppens J et al. Melanin biosynthesis in *Madurella mycetomatis* and its effect on susceptibility to itraconazole and ketoconazole. Microbes Infect 2007;9:1114–23.

11 van de Sande WW, Maghoub el S, Fahal AH et al. The mycetoma knowledge gap: identification of research priorities. PLoS Negl Trop Dis 2014;8:e2667.

12 Fahal A, Mahgoub el S, El Hassan AM et al. A new model for management of mycetoma in the Sudan. PLoS Negl Trop Dis 2014;8:e3271.

13 Murray CJ, Vos T, Lozano R et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380;2197–223.

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