



Review article

Neurologic manifestations of the neglected tropical diseases

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ARTICLE INFO

Article history:

Received 9 October 2014

Received in revised form 24 December 2014

Accepted 2 January 2015

Available online 9 January 2015

Keywords:

Central nervous system helminthiasis
 Central nervous system parasitic infections
 Central nervous system protozoal infections
 Neglected diseases
 Tropical medicine

ABSTRACT

Background: The World Health Organization has identified 17 neglected tropical diseases (NTDs) that disproportionately affect the world's poorest populations. The neurologic aspects of many of these NTDs have received relatively little attention.

Methods: A review was performed in PubMed (MedLine) for each NTD by disease name, name of its causative organism, and *neurology, neurosurgery, neurologist, brain, spinal cord, peripheral nerve, muscle, nervous system, encephalitis, meningitis, encephalopathy, stroke, neuropathy, and myopathy* (1968–Sept. 2013). The Oxford Center for Evidence-based Medicine guidelines were used to determine the level of evidence of neurological involvement and treatment based on the reports identified.

Results: Neurologic manifestations were reported for all NTDs except yaws. Neurologic involvement was described in systematic reviews for four NTDs (Chagas disease, echinococcosis, rabies, cysticercosis) (levels 2a–3a), retrospective cohort studies for six (dengue, human African trypanosomiasis, leishmaniasis, leprosy, onchocerciasis, schistosomiasis) (levels 2b–3b), case series for one (foodborne trematodiasis) (level 4), and case reports for five (Buruli ulcer, dracunculiasis, filariasis, soil-transmitted helminthes, and trachoma). Level 1 evidence for treatment of neurologic manifestations of NTDs was found for human African trypanosomiasis, leprosy, and cysticercosis and level 2 evidence exists for treatment of neurologic involvement in Chagas disease. For the remaining NTDs, treatment of neurologic complications is described in case series and case reports only.

Conclusions: Neurologic manifestations of NTDs cause significant morbidity and mortality, although limited evidence exists on how best to treat these neurologic complications. Increased awareness of neurologic manifestations of the NTDs can increase their early identification and treatment, contributing to ongoing elimination and eradication campaigns.

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1. Introduction

“Of the world’s poorest 2.7 billion people (defined as those who live on less than US\$ 2.00 a day), more than 1 billion are affected by one or more neglected tropical diseases. These diseases not only survive and spread in conditions of poverty, they also exacerbate and perpetuate the poverty of affected communities.” [1]

The World Health Organization (WHO) has identified 17 neglected tropical diseases (NTDs) that disproportionately affect the world’s poorest populations (Table 1) [1]. The NTDs cause significant disfigurement, morbidity, and mortality, accounting for 1% of the global burden of disability adjusted-life years (DALYs) lost in 2010 [2], though this is likely to be an underestimate [3]. Notably, the NTDs can be controlled – and, in some cases, eliminated or eradicated – through low-cost, strategic interventions [1]. Several international organizations advocate for the effective prevention and treatment of these illnesses, the impact of which has been deemed neglected compared to diseases such as HIV/AIDS, tuberculosis, and malaria [1]. In 2011, the London Declaration affirmed the commitment of more than twenty stakeholders, including Ministries of Health, pharmaceutical companies, United Nations agencies, and non-governmental organizations, with the goal to eliminate or eradicate ten NTDs by 2020 [4].

Although several NTDs have well-known neurologic manifestations (e.g. Chagas disease, leprosy, cysticercosis, dengue, and rabies), the neurologic aspects of several other NTDs have received less attention. The neurologic complications of the NTDs are especially important to recognize and understand among vulnerable populations, travelers, and emigrants from endemic regions. Here, we review the neurologic manifestations of each of the 17 NTDs recognized by the WHO.

2. Methods

PubMed was searched for each of the NTDs (by common name and name of the causative organism) and the search terms (free text and/or MeSH when appropriate): *neurology*, *neurosurgery*, *brain*, *spinal cord*, *peripheral nerve*, *muscle*, *nervous system*, *neurologist*, *encephalitis*, *meningitis*, *encephalopathy*, *stroke*, *neuropathy*, and *myopathy*. We also reviewed the reference lists of acquired articles to obtain sources that may not be indexed in PubMed. Articles from January 1, 1968 to September 30, 2013 in English or French were reviewed. The level of evidence was determined based on the Oxford

Center for Evidence-based Medicine guidelines [5]. For diseases for which the neurologic manifestations have been well-described in the literature (Chagas disease, cysticercosis, schistosomiasis, rabies, leprosy), mention is made of common and less common neurologic sequelae, but the reader is referred to recent reviews in the appropriate sections below.

3. Results

All NTDs are reported to affect one or more levels of the neuraxis, with the exception of yaws. Neurologic complications were reported by systematic reviews for four NTDs (Chagas disease, echinococcosis, rabies, cysticercosis) (levels 2a–3a), retrospective cohort studies for six (dengue, human African trypanosomiasis, leishmaniasis, leprosy, onchocerciasis, schistosomiasis) (levels 2b–3b), case series for one (foodborne trematodiasis) (level 4), and case reports for five (Buruli ulcer, dracunculiasis, filariasis, soil-transmitted helminthes, and trachoma). These levels of evidence may reflect both the incidence and strength of association of neurologic manifestations with particular NTDs. However, lack of access to neuroimaging, molecular diagnostics, and autopsy in endemic regions of many of the NTDs limits the ability to precisely diagnose these diseases and determine their association with neurologic complications. Level 1 evidence for the treatment of neurologic complications of NTDs exists for only three NTDs (human African trypanosomiasis, leprosy, cysticercosis), and level 2 evidence for only one NTD (Chagas disease). For the remaining NTDs, treatment of neurologic manifestations is described in case reports or case series.

4. Reported neurologic manifestations of the NTDs

The estimated global prevalence, endemic region, causative organism, vector/intermediate host, mode of transmission, non-neurologic manifestations, treatment, and control/elimination/eradication/prevention strategies for each of the NTDs are presented in Table 1. The reported neurologic manifestations are presented in Table 2. Figs. 1 and 2 present neuropathological specimens from cases of parasitic infections of the nervous system. The neurologic complications of these infections have various mechanisms including direct infection of neurons (e.g., rabies), direct infection of brain tissue with provocation of local symptoms due to mass effect and local inflammatory reaction (e.g., human African trypanosomiasis, neurocysticercosis, leishmaniasis, dracunculiasis, echinococcosis, food borne trematodiasis neuroschistosomiasis), systemic inflammatory response to the pathogen at the time of infection or the time of treatment (e.g., filariasis,

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