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Case Report: Probable Case of Spontaneous Encephalopathy Due to Loiasis and Dramatic Reduction of *Loa loa* Microfilariaemia with Prolonged Repeated Courses of Albendazole

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Abstract. Loiasis is a vector-borne parasitic disease caused by the filarial nematode *Loa loa* and transmitted by the tabanid vectors from the genus *Chrysops*. *Loa loa* infection is associated with clinical manifestations such as pruritus, migratory transient edema, passage of adult worm in the bulbar conjunctiva, retinal damage, glomerular damage, albuminuria, pleural effusion, hydrocele, and endomyocardial fibrosis. Data reporting the occurrence of spontaneous encephalopathy associated with loiasis are very scanty. Severe adverse events occurring post-ivermectin administered in the framework of the fight against onchocerciasis and/or lymphatic filariasis in loiasis co-endemic areas have been closely associated with very high *L. loa* microfilariaemia. Different regimens have been used to lower *L. loa* microfilariaemia before definitive treatment, and many discrepancies have been reported. We report the case of a patient who was admitted to a health facility and hospitalized for 34 days for altered consciousness, blurred vision, headache, and chills. After other potential diagnoses were eliminated, the patient was confirmed with encephalopathy due to loiasis and referred to the Centre for Research on Filariasis and other Tropical Diseases (CRFilMT). On admission at CRFilMT, the patient was harboring 28,700 microfilariae per milliliter of blood (mf/mL), and after four 21-day courses of 400 mg daily albendazole, the *L. loa* microfilariaemia lowered to 5,060 mf/mL. The patient was then treated with ivermectin 3 mg and a total clearance of microfilariae was observed, with satisfactory clinical evolution and no adverse event. This case study further confirmed that albendazole is effective against *L. loa*, but might necessitate a longer course.

INTRODUCTION

Loiasis is a filarial infection found in Central and West Africa and affecting millions of individuals, with prevalence up to 50% in some highly endemic areas.[1–4] Loiasis is transmitted by the tabanid vectors from the genus *Chrysops*, commonly called deer flies, horse flies, stouts, mango, or mangrove flies.[5] Although some studies have revealed *Loa loa* microfilariae (mf) in night blood smears, these last years both in Cameroon and Democratic Republic of the Congo (DRC),[6,7] *L. loa* mf exhibit diurnal periodicity with mf counts peaking during mid-day, adapted to the feeding habits of *Chrysops*. Larvae penetrate the stomach of the fly and locate to the fat body. About 8–10 days later, the infective L3 larvae migrate to the cavity of the biting mouthparts and are released into the bite wound when the fly takes another blood meal. The larvae develop slowly, in the subcutaneous tissues of the host, into adults within 1–4 years. Mature worms mate and the females begin laying mf. The adult worms can live in the tissue for up to 17 years.[8]

Loiasis is exclusively transmitted in Africa, particularly in the forested areas of Central and West Africa.[1,9] A survey carried out by the African Program for Onchocerciasis Control using the rapid assessment procedure for loiasis strategy had shown that the disease is found in two large foci with high prevalence: 1) the west focus covering the South East Nigeria, the South of Cameroon, Equatorial Guinea, Gabon, west of Congo, the Coastal Plains of Angola, the Bas Congo in DRC, the west of Central African Republic (CAR), and the South of Chad. 2) The East focus covers the east of CAR, the South Sudan, the North East of DRC, and small foci found at the boundary between Kenya and Sudan.[9,10]

Loiasis was reported in some endemic regions as one of the main causes of medical consultations.[11] Visitors and expatriates living in endemic areas present with more clinical signs after infection than the natives who harbor high microfilarial load.[5] Clinical manifestations of loiasis include Calabar swellings preceded by pain and itching (non-erythematous, angioedematous swellings), eye lesions, renal disease, arthritis, lymphadenitis, cardiomyopathy, neuropathy, encephalitis, pleural effusion, hydrocele, and the passage of the adult worm across the bulbar conjunctiva of the eye.[12,13] Although some drugs are effective against *L. loa*, no control program is dedicated to this disease because 1) this filarial disease has historically been considered benign and 2) severe adverse events (SAEs) have been reported after ivermectin or diethylcarbamazine treatment primarily in those individuals harboring *L. Loa* microfilariaemia higher than 30,000 mf/mL of blood.[14] Encephalopathy is a common complication of systemic illness or direct brain injury. It can manifest as a spectrum that begins with subtle cognitive changes, progresses as a full-blown syndrome of brain dysfunction, and eventually leads to coma or brain death.[15] Loiasis encephalopathy may occur either spontaneously or following chemotherapy targeting *L. loa*.[16] A number of drugs have been tentatively used to lower *L. loa* microfilarial loads below levels at which patients are at risk for SAEs before using a more powerful or definite therapy (ivermectin or diethylcarbamazine).[17–23] Albendazole appeared as the only promising drug not leading to SAEs, although very high variations have been observed in *L. loa* mf decreasing, and a consensus regimen was yet to be found.

In this article, we report a case referred to the Centre for Research on Filariasis and other Tropical Diseases (CRFilMT) for meningoencephalitis due to *L. loa* without prior intake of any antifilarial drug, treated and followed up using long courses of 400 mg albendazole.

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CASE REPORT

A 36-year-old watchman, native of Touboro (North Region, Cameroon) and residing in Yaounde (Centre Region, Cameroon) for more than 5 years, was admitted in The Military Hospital in Yaounde on June 28, 2016, for altered consciousness, asthenia, headache, chills, blurred vision, and difficulties speaking. Clinical evaluation indeed revealed altered consciousness (Glasgow Coma Scale [GCS]: 11/15, $E_4V_3M_4$), stable hemodynamic parameters, conjunctiva pink over lower lids, anicteric sclerae, dry lips, normal cardiopulmonary system, and normal digestive system. The presumptive diagnosis on entry was cerebral toxoplasmosis. He was admitted in the hospital and treated with injectable antimalarial (artemether), analgesia, intravenous fluids, and pyrimethamine with monitoring of vital parameters. Blood analyses revealed the presence of hemoparasites (640 trophozoites/mm^3), stool analysis revealed the presence of *Ascaris lumbricoides*, and serological analyses were nonreactive to toxoplasmosis, Widal reactive, Human Immunodeficiency Virus nonreactive, and C-Reactive Protein was elevated (48 mg/L). On day 2 post-hospitalization, head computed tomography was performed and the result was normal. The presumptive diagnosis of toxoplasmosis was then rejected and the management was adjusted with injectable antibiotics for suspicion of meningoencephalitis. A slight amelioration of the GCS (12/15, $E_4V_2M_6$) was then observed although the general state was still altered. Day 6 post-hospitalization was marked by decreased consciousness (GCS: 8/15, $E_3V_2M_3$), and the patient was transferred to the intensive care unit, where lumbar puncture performed was sterile; full blood count revealed 9,200 white blood cells among which 19% were eosinophils and subsequent calibrated thick blood film performed by a laboratory in Yaounde revealed the presence of *L. loa* mf with an intensity of infection of 25,600 mf/mL. Malaria parasites were no longer found in both the thin and thick blood smears. Seventeen days post-hospitalization, the GCS increased from 8/15 to 11/15 and the blood pressure raised to 155/113 mm of Hg. The patient was further transferred to internal medicine where he was managed with albendazole 400 mg daily for 5 days, with antihypertensive, antibiotics, gastric protectors, mannitol, and laxatives. The patient was hospitalized for 34 days and managed multidisciplinary. He was discharged with mildly altered state of consciousness (GCS 12/15) and slightly altered general state. Although discharged, the patient underwent retinography, which revealed pigmented chronic retinitis.

One day following his discharge, the patient was referred to the CRFilMT for the management of meningoencephalitis due to *L. loa*. Calibrated thick blood smear indeed revealed an intensity of infection of 28,700 mf/mL on arrival at the CRFilMT; this high *L. loa* level was confirmed 9 days later using a newly developed point-of-care diagnostic tool, the Loa-Scope that revealed microfilarial load of 28,736 mf/mL. Loa-Scope was used for subsequent follow-up of *L. loa* intensity of infection. After a 3-week course of 400 mg daily albendazole regimen, the microfilariaemia was lowered to 21,344 mf/mL, with satisfactory clinical evolution (GCS 15/15, good general state, could walk alone). The next day following the first 3-week treatment, a second regimen of albendazole 400 mg daily for 21 days was given, and control examination performed 3 months later revealed a decrease in *L. loa* microfilarial load (16,453 mf/mL) with favorable clinical evolution. Third course of albendazole 400 mg daily for 21 days lowered the *L. loa* microfilariaemia to 10,639 mf/mL and the fourth course lowered to 5,221 mf/mL (5,060 mf/mL using calibrated blood smear), and the general state of health was stable. The vision clinically improved and the patient could walk more easily. No side effect was registered during the follow-up of the patient. As any ivermectin/diethylcarbamazine–associated SAE was not expected at this mf load, one tablet of ivermectin 3 mg (1/4 of the full dose) was given to the patient because the patient was just recovering from an encephalopathy. A subsequent reduction in microfilarial load (from 5,060 to 1,119 mf/mL) was observed after 1 month of follow-up. Finally, a full dose of ivermectin (150 μg/kg) (four tablets) was given as a regular, optimal therapy, and the follow-up 3 months later showed a total clearance (0 mf/mL) of *L. loa* mf in the blood. At this stage, the patient was clinically in good state of health, with a normal GCS (15/15) and the faculty to easily walk alone and recognize objects.

DISCUSSION

Encephalopathy associated with loiasis is mostly observed post-ivermectin treatment and occur particularly among patients harboring high *L. loa* microfilariaemia (more than 30,000 mf/mL).[14] This usually occurs in areas where loiasis is co-endemic with onchocerciasis and/or lymphatic filariasis whereby community-directed treatment with ivermectin is implemented. Previous findings have shown that retinal hemorrhage is often associated with post-ivermectin encephalopathy on funduscopic examination.[24] Encephalopathy is qualified spontaneous when there are signs of central nervous system involvement without prior antifilarial treatment. These involvements can, in certain circumstances, be due to loiasis. The report of the present case is similar with some previous findings where high loiasis microfilariaemia (> 30,000 mf/mL) was associated with spontaneous coma.[25] Our patient was also diagnosed with malaria (severe malaria is also amenable to provoke impaired consciousness),[26,27] but his general state deteriorated despite administration of antimalarial drugs and clearance of parasitaemia, thus excluding the likelihood of malaria involvement in the spontaneous coma observed. Importantly, although the patient presented with loss of consciousness for about 5 weeks with high microfilariaemia, he regained consciousness and his daily activities following appropriate treatment, contrary to previous reports.[28,29] Some authors have raised concerns about the mechanism of occurrence of sudden encephalopathy associated with loiasis; it was proposed that other conditions (malaria, meningitis, etc.) likely acting on the blood–brain barrier might lead to lesions at the vascular level, thus facilitating the passage of mf into the brain tissue as was previously reported.[28,29] Our patient presented with signs of raised intracranial pressure, the presumptive diagnosis being cerebral toxoplasmosis associated with severe malaria. Despite administration of optimal and appropriate symptomatic treatments, symptoms persisted until 6 days following hospitalization when he was diagnosed with high loiasis microfilariaemia.

The diagnosis of loiasis was confirmed on arrival at the CRFilMT, and the patient was submitted to albendazole 400-mg regimen daily for 21 days. After four 21-day courses of albendazole, the *L. loa* microfilarial load decreased by 82.4%

with amelioration of the patient's clinical state. These findings confirm that albendazole is effective against *L. loa* as was previously demonstrated.[20,21] The decrease in microfilarial densities observed in the present case was more marked than in previous studies using shorter courses of treatment.[19,20] As a consequence to SAEs occurring post-ivermectin treatment, loiasis remains a major barrier for the elimination of onchocerciasis and lymphatic filariasis.[10,14,30] It was proposed that a pretreatment can be used to lower *L. loa* mf densities under the threshold associated with SAEs, before using a definite treatment. In the present case, thanks to longer regimens of daily albendazole 400 mg, *L. loa* mf densities have been safely lowered far below the threshold at which ivermectin can be safely used, contrary to other antifilarial and antimalarial drugs that have previously been studied for this purpose.[17,18] Indeed, one quarter dose of ivermectin was given to the patient when his *L. loa* microfilarial load dropped to 5,060 mf/mL, as was previously tested in previous clinical trials investigating the efficacy of low doses of ivermectin on loiasis.[18,31] A subsequent reduction in microfilarial load (from 5,060 to 1,119 mf/mL) was observed after 1 month of follow-up, and finally a full dose of ivermectin (150 μg/kg) was given as a regular patient, with follow-up scheduled every 6 months, as to previous findings.[32] The safe *L. loa* microfilarial density threshold below which ivermectin can be safely administered is 20,000 mf/mL,[33] meaning that our patient would have been eligible to ivermectin just after two 21-day courses of albendazole. However, this patient was not treated with ivermectin after two courses of albendazole because he was just recovering from an encephalopathy. Actually, a new strategy, Test and Not Treat, has been developed to fight against hypo-onchocerciasis and lymphatic filariasis in areas where loiasis is co-endemic. The principle of this strategy is to use a newly designed point of care tool, the LoaScope,[34] to identify individuals harboring mf densities above at-risk threshold for SAEs, exclude them from treatments, and treat the rest of the population either for onchocerciasis or lymphatic filariasis. This strategy was successfully used in the Okola health district in Cameroon, known to be hypo-endemic for onchocerciasis and endemic for loiasis, without any SAE following ivermectin administration.[33] However, those individuals excluded from treatments still harbor loiasis and, particularly, at high microfilarial load (greater than 20,000 mf/mL). There is growing evidence regarding the clinical impact of loiasis,[10,35] suggesting that this disease should not be under-considered as it is the case until now. Because research is now advocating to consider loiasis among the neglected tropical diseases necessitating an intervention, it appears of high importance to identify drugs for safe treatment of this filarial infection and develop a control program dedicated to this disease. Long-course albendazole regimen can be useful, at least for individual treatment, to lower *L. loa* mf load before a definite treatment. Research is therefore highly needed to develop a safe and effective treatment against loiasis and that can be used in the framework of mass treatments.

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