Loiasis: bringing an end to neglect

Loa loa infections affect up to 20 million people in Central and West Africa, but options for treatment and control are widely inadequate. Laura Salm-Reifferscheidt reports.

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José Mouanga Ma is setting up flytraps on the banks of the Ngounie River near Sindara, a village in the rainforest in Gabon. He recounts the moment, 30 years ago, when he first felt a stabbing pain in his eye. He ran to his father, asking him to have a look. "A worm, a little worm is moving in your eye!", the 45-year-old remembers his father exclaiming.

"I was scared. I thought I might lose my eye because it hurt so much", recalls Ma. Since then, every few weeks, a worm has migrated through his bulbar conjunctiva. Sometimes it only passes through one eye, sometimes through both. The migration might take a few hours or up to 2 days. Ma has had other symptoms, too: unbearable itching all over his body, fatigue, headaches, and swollen and painful ankles, sometimes for days.

Ma suffers from loiasis, a chronic filarial disease caused by the *Loa loa* parasite, also known as the African eye worm for exactly the reasons he describes. The larvae of the worms are transmitted to humans through the bite of deer flies (*Chrysops* spp). Living in the dense tree canopies, the flies are attracted to fire, movement by humans, and colours. The disease mainly affects rural populations in the forest and savannah regions of Central and West Africa, where, according to latest estimates, up to 20 million people are infected.

Despite his symptoms, until recently Ma had never seen a doctor for the condition. There are no national control programmes for loiasis in endemic countries as there are for other filarial infections such as onchocerciasis. This absence of control programmes might be because loiasis was long seen as both benign and difficult to treat. Dr Rella Zoleko-Manego, from the Gabonese research institute Centre de Recherches Médicales de Lambaréné (CERMEL), recalls being taught at university that it would be better to simply not give any medication at all. "So when I saw the patient, I [only said], 'there is no treatment, please go back home'."

Compared with malaria, loiasis is not an acute disease that kills in a matter of weeks, explains Zoleko-Manego. However, since she started working with the disease, it has become clear that loiasis has serious consequences for affected individuals. "We might have never experienced an eye worm migration, but it is very painful. Some people rub chilli in their eye because it is so painful and they want to kill the worm", she told *The Lancet*.

Zoleko-Manego heads the Institut de Recherches en Santé de Sindara, a small loiasis research centre set up on a hill overlooking the village below and the sprawling rainforest beyond. Located a couple of hours' drive from the town of Lambaréné, the institute was established 2 years ago as a collaboration between the Bernhard Nocht Institute for Tropical Medicine (Hamburg, Germany), and CERMEL, the former medical research unit of the Albert Schweitzer Hospital, founded in 1913 by the Franco-German doctor and theologian after whom the hospital is named. Sindara proved to be an ideal location for loiasis research: according to epidemiological surveys, in some villages in the area more than 70% of the adult population is infected.

When Dr Lilian Endamne first started working at the Sindara site, he was surprised by the local population's knowledge of loiasis. They knew the symptoms of the disease and what could be done about it, albeit with non-curative traditional methods, such as herbal remedies or using a thorn to pluck the worm from the eye. Now, Endamne says, "When they have symptoms, they come here by themselves, with the diagnosis on their tongue. That's good because it is these [individuals] who help us to understand the disease better."

There were challenges to overcome in the beginning because some patients were afraid to give the regular blood samples required for the centre's research, worrying that they would

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Dr Lilian Endamne with a loiasis study participant during a consultation at the CERMEL research station.

be used for nefarious purposes. "They took us for vampires", says Endamne, only half-jokingly. Eventually, with a great deal of explaining, the team was able to build trust. Many of the research station staff hail from the surrounding villages and could help dispel myths. It helps, too, that treatment is free of charge, and not only for loiasis but for any kind of ailment: malaria, tuberculosis, bilharzia, diarrhoeal diseases, and helminth infections are all prevalent in the region.

Now, there is a constant stream of people waiting to see a doctor. Many of the individuals with loiasis are participating in clinical trials to assess the therapeutic possibilities of existing medications. Studies involving molecules used in veterinary medications adapted for use in humans are also underway. Individuals present with the whole range of symptoms. Many have experienced the painful migration of the worm through the eyes, and so-called Calabar swellings, usually near joints but sometimes on the face. Others can see the worm crawling beneath their skin. Then, of course, there is the itching, the fatigue, and the headaches. Showing his swollen wrist, one individual says he is unable to clear his fields because it is too painful to hold a machete. The majority of the area's residents are fishers or subsistence farmers.

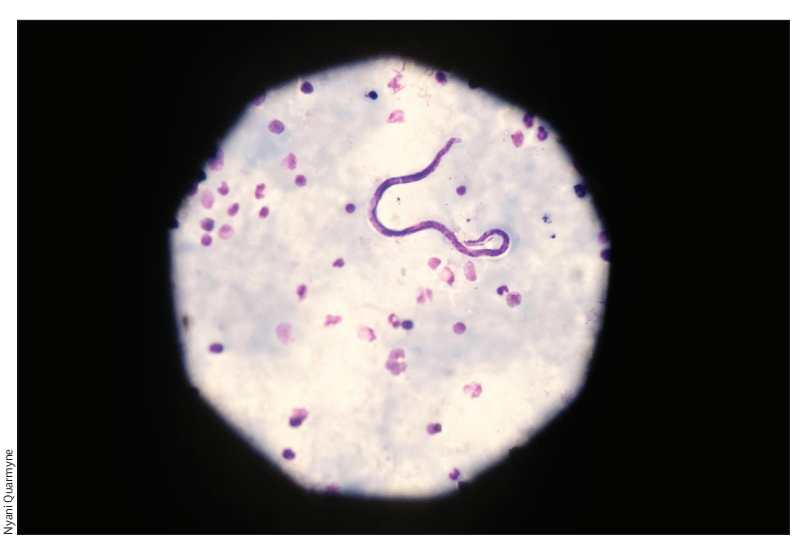
One of the studies currently underway seeks to quantify the economic repercussions of loiasis: how much does it cost individuals to buy medication or to travel to a hospital, and what are the impacts of not being able to farm or to take care of the children? It is a complex task, says Michael Ramharter from Bernhard Nocht Institute for Tropical Medicine, a co-founder of the Sindara centre who has been working in Gabon for 25 years. "When you have a disease and the health system does not offer you a solution, then you initially have zero direct costs, because the patient says, 'I won't even go there'. However, that does not reflect the reality, because the patient is willing to spend money to be treated. So he goes to a traditional healer instead and invests his time and money there."

In the laboratory next to Endamne's consulting room, technician Diane Dada Msoutsou looks through her microscope at something that remains an endless source of fascination: a tiny worm—or microfilaria—is wriggling past red blood cells "like a little snake". Although the adult worms crawl across the eyes and through subcutaneous tissues, the microfilariae—their offspring—are bloodborne. During the day, when temperatures are high, the microfilariae move to capillaries close to the surface of the skin, where they are ingested by female *Chrysops* flies seeking a blood meal. Within the fly, the microfilariae evolve into the infectious larval stage, ready once again to be transmitted to a human through the insect's bite. This time, they develop into adult worms that ultimately produce further microfilariae—a never-ending cycle.

Msoutsou has seen blood samples teeming with so many microfilariae that she could not count them. It is not unknown for more than 100 000 microfilariae to be found in a single millilitre of blood. Extrapolating this to the roughly 5 L of blood in the average adult human body, "you can imagine what kind of biomass is swimming around in the bloodstream", says Ramharter. Recent studies attribute an excess mortality of 14·5% to loiasis, and although there is still much to understand, researchers believe this might be due to microfilariae provoking an immune reaction in the body that leads to heart, lung, and kidney damage and, in the long run, death.

However, microfilariae are only found in the blood of one-third of individuals with loiasis; the majority suffer from what is known as occult loiasis. This hidden clinical variation of the disease can only be diagnosed with certainty through the migration of the adult worm across the eye. Just how many adult worms might be in a person's body at any given time is not known; it might be a dozen, it might be hundreds, says Ramharter. Considering that the worms have a lifespan of up to 20 years and that people in highly endemic areas are almost certainly infected multiple times, these people are likely to carry *Loa loa* throughout their entire adult lives.

Further complicating diagnosis and treatment is the fact that not all people with loiasis are symptomatic. Thus, explains Ramharter, someone who has no symptoms from the adult worm, but who has a high microfilarial load,



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***Loa loa* microfilaria.**

will probably never notice the infection but may later suffer from organ complications.

Regardless, what treatments currently exist— ivermectin, diethylcarbamazine, and albendazole—are inadequate. "We have medications that are 80, 90 years old which come with risks; or others you have to take for a very, very long time, such as 3 or 6 weeks", which, explains Ramharter, is a challenge in rural areas without health facilities. There are no medications to stop transmission in a way that is safe for patients.

That some medications are risky for those infected with *Loa loa* was discovered by accident in the early 1990s. Mass drug administration programmes were being established to combat onchocerciasis, which causes blindness. The antiparasitic ivermectin was found to be effective against onchocerciasis and was distributed widely in affected regions. Then, in Cameroon, unexpected deaths occurred. It transpired that, in addition to onchocerciasis, the deceased had very high levels of *Loa loa* microfilaraemia. "Ivermectin paralyses these [*Loa loa*] larvae", explains Sabine Specht, Head of Filarial Disease at the Drugs for Neglected Diseases initiative, "and that happens mostly within 24 h after taking the medication. When the microfilarial load is so high it can lead to a very strong immune reaction, changes in the cerebral microcirculation, and parasites crossing the blood–brain barrier, and consequently to encephalopathy."

Mass drug administration programmes in co-endemic regions with a high prevalence of both diseases were stopped, impeding the elimination of onchocerciasis. According to Maria Rebollo Polo, Lead of the Global Onchocerciasis Elimination Program at WHO, "Gabon has not even started the fight against onchocerciasis, exclusively because of loiasis and the danger of using ivermectin. So if there were a control, even a vector control for *Loa loa,* it would already make a massive difference." However, she adds, loiasis itself requires attention.

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Swollen joints are a common symptom of loiasis

Unlike onchocerciasis, loiasis has not made it onto the WHO list of neglected tropical diseases, which recognises 21 diseases as requiring urgent public health attention. Although it is up to member states to request that a specific disease be considered for inclusion on the list, Rebollo Polo hopes that loiasis will be included in the future. "I have lived for many years in the forest in Cameroon and the Congo. And I can tell you that *Loa loa* produces a lot of morbidity."

Research by Ramharter and Zoleko-Manego supports this and indicates that the burden of disease resulting from loiasis in Gabon is similar to that from schistosomiasis, which is a listed neglected tropical disease. In Ramharter's view, "it is a major barrier that loiasis is not on this list, because it defines the priorities of donors, those of the WHO, and ultimately those of national control programmes".

In Sindara, drug regimens are being trialled in the hope of finding a therapy that can be deployed at scale while avoiding the risks arising from a mass die-off of microfilariae. In addition, explains Ramharter, they are incorporating new endpoints into their studies that focus on the subjective feelings of the individuals: does the individual really "feel better after being treated or is it perhaps the case that the parasitologist says, 'Great, we have cured [the affected individual]', but ultimately he feels the same as before?"

There are also challenges that cannot be addressed through clinical trials and research. "We are neglected by the government", says Ma. "We don't have a road, we don't have a dispensary, we don't have electricity." There is also no running water and there are no jobs, he adds. The nearest hospital is 30 km away. In such a context, research comes with responsibility, says Endamne: "We cannot work here without taking social issues into account because we experience poverty every day … Infectious diseases are not even a medical problem here; it is about solving the problems of poverty. That is what hurts us the most because we are powerless against it."

So the team continues to treat not only *Loa loa* patients free of charge, but anybody else who is sick. Ma returns to his flytraps. He took part in a trial to test an existing medication himself; he feels much better. Besides that, he is happy to have found a role at the centre trapping *Chrysops* flies to support research on the transmission and development of *Loa loa* larvae. "I am proud of this work", he says. "It is good to help the people of Sindara."

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