

THREE PROBABLE CASES OF *LOA LOA* ENCEPHALOPATHY FOLLOWING IVERMECTIN TREATMENT FOR ONCHOCERCIASIS

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Abstract. Over the past nine years, more than 12 million people exposed to *Onchocerca volvulus* infection have received at least one dose of ivermectin, almost all without serious adverse reactions. Since 1991, however, several cases with neurologic manifestations, including coma, have been reported after ivermectin treatment of persons infected with *O. volvulus* who also had concomitant *Loa loa* infection with very high microfilaremia (> 50,000 microfilariae/ml of blood). In 1995, four criteria were established to define probable cases of *Loa* encephalopathy temporally related to treatment with ivermectin (PLERI). The present paper describes three PLERI cases recorded in Cameroon and compares them with two others reported previously. Disorders of consciousness began 3-4 days after treatment. The objective neurologic signs were variable. The conditions improved favorably in three patients who benefited from early hospitalization and good nursing; their disorders of consciousness lasted only 2-3 days; the results of clinical examination became normal after one month and electroencephalographic abnormalities disappeared after 5-7 months. Conversely, late diagnosis and delay in proper management in two others probably led to worsening of the condition and to fatal outcome related to the usual complications of coma. In addition to these cases, patients with high *Loa* microfilaremia also developed milder neurologic manifestations causing functional impairment lasting for at least one week after treatment. Before launching mass ivermectin distribution programs to control onchocerciasis in central Africa, communities in which the intensity of concomitant *L. loa* microfilaremia is high need to be identified, and specific educational measures and monitoring strategies should be developed and applied before they are treated.

Mass ivermectin (Mectizan®; Merck and Co., Inc., Whitehouse Station, NJ) distribution programs (IDPs) against onchocerciasis are currently being developed in most African countries where the disease is endemic. Since 1989, several studies have shown that ivermectin is generally well-tolerated by patients infected with *Loa loa*,¹⁻⁵ and consequently IDPs were extended to forested areas in central Africa where loiasis is coendemic with onchocerciasis. In 1991, the first case of encephalopathy following ivermectin treatment was recorded in Cameroon in a patient with *L. loa* microfilariae (mf) in both the blood and the cerebrospinal fluid (CSF).⁶ Since similar events have been known to occur after treatment of loiasis with diethylcarbamazine (DEC), the hypothesis was proposed that ivermectin might also induce serious neurologic reactions in patients with high *L. loa* microfilaremia.⁷ Following the report of two other suspect cases in southern Cameroon,⁸ a clinical study of reactions to ivermectin treatment was carried out in the Central Hospital in Yaounde, Cameroon on 112 patients with *L. loa* microfilaremia exceeding 3,000 mf/ml. This study showed that ivermectin may provoke the passage of *L. loa* mf into the CSF. In addition, during this study, another case of *L. loa* encephalopathy was recorded.⁹ This paper reports three new probable cases of *L. loa* encephalopathy occurring after ivermectin treatment between June 1995 and February 1996, and provides information on 20 other cases of severe functional impairment, without disorders of consciousness, which also occurred after treatment.

METHODS

Study area. All the cases were recorded in the Lekie Division of central Cameroon. This densely populated forest area lies along the left (south) bank of the middle section of the Sanaga River, where 40-95% of the residents had *On-*

chocerca volvulus mf in the skin and 10-33% had *L. loa* microfilaremia (Boussinesq M and others, unpublished data). The Lekie Division is also endemic for *Mansonella perstans*, but not for lymphatic filariasis.

Case definition. As previously indicated, some reports were available by mid-1995 on adverse neurologic events in an area of Cameroon that was endemic for both loiasis and onchocerciasis, and where IDPs were underway. This resulted in the Mectizan® Donation Program organizing a meeting in Paris to review all existing data on *Loa* encephalopathy, including the cases recorded after treatment with ivermectin (Central nervous system [CNS] Complications of Loiasis and Adverse CNS Events Following Treatment—Report of an Invited Consultation: October 2-3, 1995). During this meeting, expert clinicians, pathologists, epidemiologists, and parasitologists defined a probable case of *Loa* encephalopathy temporally related to treatment with ivermectin (PLERI) as having satisfied four criteria: 1) occurrence of a coma in a person who was previously healthy, and who has no other underlying cause for the coma; 2) onset of the CNS symptoms and signs within five days of ivermectin treatment and progression to coma without remission; 3) very high *Loa* microfilaremia, i.e., $\geq 10,000$ mf/ml, if the blood sample had been obtained before treatment, or $\geq 1,000$ mf/ml if the blood sample had been collected within the two months following treatment; the latter threshold value was adopted following the results of small-scale trials that showed that post-treatment *Loa* microfilaremia is approximately 10% of the pretreatment level; and 4) the presence of *Loa* mf in the CSF.

Case recording and pretreatment examinations. All the cases described in the present report were recorded after first ivermectin treatment at dose of 150 µg/kg of body weight. Three patients developed serious neurologic manifestations. Case 1 had been routinely treated during an IDP carried out by a nongovernmental organization; thus, no pretreatment



observations were made on this case. Cases 2 and 3 were recorded during an incidence study (ethically approved by the World Health Organization and the Cameroon Ministry of Health and involving 17,877 persons) aimed at determining 1) the incidence of serious neurologic reactions during the week following ivermectin treatment in an area where onchocerciasis and loiasis are coendemic, and 2) whether any relationship exists between the occurrence of serious neurologic reactions and the presence of intense *Loa* microfilaremia in treated patients.¹⁰ Before distribution of ivermectin, the patients involved in this incidence study were informed that reactions might occur during the days immediately following treatment, that they would be visited daily for the first seven days after treatment, and that any reaction will be treated free of charge. Monitoring of side effects was performed by physicians with the assistance of selected residents who were asked to visit all households to record possible serious reactions. In addition to the neurologic reactions, 20 patients of the 17,877 treated during the incidence study developed a less serious condition characterized by severe functional impairment, but without disorders of consciousness or objective neurologic signs. This impairment was such that for several days they could not carry out any of their everyday domestic activities without assistance. This condition will be referred to as a serious non-neurologic reaction.

Blood smears were taken just before dosing from all persons 15 years of age or older in this incidence study; no skin snips were taken before treatment. The smears were made from 50 μ l of capillary blood collected by fingerprick between 10:00 AM and 4:00 PM and were stained with Giemsa. These smears were examined subsequent to treatment and the microfilarial loads were expressed as mf/ml of blood. No other blood samples and no skin snips were taken before treatment. Among the 5,550 adults who underwent a blood smear examination and had never received previous filaricidal treatment, the prevalence of *Loa* microfilaremia was 29.9%.

Laboratory examinations made after the appearance of adverse manifestations. These examinations were limited to the three patients who developed serious neurologic reactions (cases 1, 2, and 3). The day of treatment was D0 and the subsequent days were designated D1, D2, and D3, etc.

Venous blood was taken and capillary blood smears were made (between 10:00 AM and 4:00 PM) on D13 for case 1, and on D4 and D7 for cases 2 and 3. The laboratory examinations included complete blood counts, calculation of mf concentrations, determination of plasma electrolytes, glucose, creatinine, proteins, transaminases (aspartate aminotransferase and alanine aminotransferase), creatine phosphokinase (CPK), C reactive protein (CRP), alkaline phosphatase, complement C3, and protein electrophoresis. In addition, hemoglobin electrophoresis was performed in cases 2 and 3 to determine whether the patients had sickle cell disease; this investigation was done because it was assumed that *Loa* encephalopathy was at least partly related to an obstruction of the cerebral vessels secondary to the death of mf, and sickle cell disease might constitute a cofactor facilitating the pathologic process. Three milliliters of CSF were collected on D13 from case 1, and on D4 from cases 2 and

3. One milliliter was used for counts of red blood cells and leukocytes, and for determination of glucose, protein, and chlorides levels. One milliliter was centrifuged at $1,235 \times g$ for 15 min and the mf in the pellet were counted. Urine samples were collected on D13 from case 1, on D4 and D7 from case 2, and on D7 from case 3. Ten milliliters were centrifuged at $4,750 \times g$ for 5 min and the mf in the sediment were counted. The remainder of each sample was used for counts of red blood cells and leukocytes and for determination of glucose and protein levels. Electroencephalograms (EEGs) were performed on case 2 (on D15, D146, and D233) and on case 3 (on D19, D105, and D159) by Professor G. Atchou of the General Hospital in Yaounde.

CASE DESCRIPTIONS

The main clinical findings in the three PLERI cases described here are listed in Table 1. To evaluate whether common features exist between all cases that meet the criteria of PLERI, the clinical findings of the three cases described in detail in this paper are compared in Table 1 with the findings from the two previous cases recorded in the literature.^{6,9} The biological findings from the same five PLERI cases are listed in Table 2.

Case 1. This patient was 26-year-old male farmer living in Okok (4°08'N, 11°15'E). Ten hours after treatment on D0 he complained of backache, neck pain, and tinnitus. On D1 he had stomach pains and diarrhea. On D2 and D3 he was very weak, unable to remain standing or to eat, and his neck was stiff. On D4 he had difficulty in swallowing and speaking, and he was taken to a health center. On D5, he did not speak, became incontinent of urine, and his temperature was 37.4°C. Treatment was started, including perfusion with glucose, dexamethasone, atropine, furosemide, and diazepam. On D6 he became comatose until D9 when his fever increased to 38.5°C and penicillin and tube feeding were added to his treatment. His condition remained unchanged until he was hospitalized on D13. Between D13 and D16, he did not respond to commands or to painful stimuli; his eyes were open and corneal reflexes were present, tendon reflexes were absent and there was no Babinski sign, his neck was stiff, he showed signs of dehydration, and had large bedsores on the buttocks. Treatment included glucose infusion, intravenous betamethasone, tube feeding, and treatment of his bedsores. On D17, the condition improved slightly, with the patient being able to perform voluntary movements of the eyes, fingers, and legs. On D18, his condition worsened and his temperature increased because of a large abscess on one cheek. The betamethasone was discontinued and replaced with ampicillin and gentamicin, but he died on D21.

On D13 (Table 2) his counts of *L. loa*, and *M. perstans* mf in capillary blood were 3,600 mf/ml and 960 mf/ml, respectively, there was no eosinophilia, and the CRP and CPK levels were very high. The CSF was clear, with 10 live *Loa* mf/ml, and the protein level slightly elevated. *Loa* mf were also found in the urine. The other results were normal.

Case 2. The patient was 32-year-old male farmer living in Mbazoa (4°20'N, 11°27'E) and had no relevant medical history except for chronic alcoholism. On D1 he was weak and anorexic but was able to walk. On D2 he stayed in bed and did not speak. On D3 he became feverish, which was

TABLE 1

Clinical signs in the five probable cases of *Loa loa* encephalopathy temporally related to ivermectin treatment recorded from 1991 to 1996 in Cameroon*

	Anonymous ⁶	Ducorps and others ⁹	Case 1	Case 2	Case 3
Sex, age (years)	M, 37	M, 40	M, 26	M, 32	M, 18
Village	Pouma	Obala	Okok	Mbazona	Nkolobang
Hospitalization period (days)	4-24	0-27	13-21	4-13	4-14
Condition on day 1	Dizziness, headache	Joint pains, headache	Joint pains, stomach pain, diarrhoea	Dizziness, anorexia	Joint pains
Condition on day 2	Dizziness, headache	Joint pains, headache, diarrhoea	Dizziness ++, anorexia	Dizziness ++, mutism	Dizziness
Condition on day 3	Dizziness, headache, dysarthria	Dizziness, confusion	Dizziness ++, anorexia	Dizziness ++, mutism, fever	Coma, mutism, incontinence
Worst Glasgow score	8 (D5)	8-9 (D4)	6	10 (D4-5)	5-6 (D4)
Fever $\geq 38.5^{\circ}\text{C}$	D19-23	D1	D9	D3	No
Mutism	D5-15	D4-5	D5-21	D2-6	D5-6
Involuntary movements	No	No	No	D4-11	No
Agitation	No	Yes	No	D4-6	No
Motor deficit	No	No	Yes (++++)	D9-10	D3-7
Sensitivity deficit	No	No	Yes (++++)	D5; D8-13	D4-5
Paresthesia	No	No	?	No	D9-10
Tendon reflexes	Normal	Abolished (D3-8)	Abolished	Brisk (D4-11)	Abolished (D4)
Babinski's sign	No	No	No	No	No
Grasping reflex	?	No	?	D4-5	No
Hypertonia	No	No	?	D5-10	D4-7
Cogwheel phenomenon	?	?	?	D5; D8-27	D4-21
Meningeal signs	No	No	Yes	No	No
Incontinence	?	D5†	D5†	D5-6	D3-9
Treatment	Tube-feeding, antibiotics, corticosteroids	Perfusion, lorazepam, furosemide	Perfusion, antibiotics, corticosteroids	Antihistamines, paracetamol	Perfusion, tetracycline, antibiotics
Outcome	Death	Recovery	Death	Recovery	Recovery

* D = days; ++ = marked; +++ = important.

† D5 is the day of appearance of incontinence; the day of disappearance was not recorded.

attributed to malaria and he was given chloroquine. On D4 his condition worsened and he was hospitalized. At this time, his temperature was 37°C , he was unable to stand, and was alternatively somnolent and restless. The general condition of the joints was in flexion. He answered only yes or no to questions, but in an incoherent manner; otherwise, he did not speak at all. On command, he did not perform any voluntary movement. The pain sensation was normal, the corneal reflexes were feeble, the pupillary reflexes were normal, tendon reflexes were very brisk and symmetric, and plantar responses were flexor. He showed shaking of hands, and crumbling, dusting, and scratching movements. He had a marked grasp reflex. There were no meningeal signs or hypertonia. Treatment with paracetamol and chlorpheniramine maleate was given. On the evening of D4, the patient was able to perform adjusted simple movements on command, and a spastic hypertonia with the clasp-knife phenomenon was found. On D5 his condition was similar but he became incontinent and did not speak; surprisingly, he was able to hold a glass and to drink without help, and when a flashlight was given to him, he switched it on and off, but without regard to the examiner's command. His Glasgow coma score was 10; a cogwheel phenomenon had appeared at the wrists, elbows, and knees; pain sensation varied from second to second, with sometimes no response to pinching. On the morning of D6 he was still somnolent, incontinent, and unable to speak or walk. In the evening his condition improved considerably and he could walk with assistance, speak spontaneously, respond to commands and recognize his relatives; however, his face remained inexpressive. Episodically, he

showed flexion attitude of the upper limbs, and involuntary movements appeared when he had to perform a mental effort. His condition from then on improved progressively. On D7 he could walk slowly with short steps but without help, and a fundus examination showed bilateral retinal hemorrhages. On D8 and D9 involuntary movements became less frequent but the cogwheel phenomenon persisted at the wrists and elbows, and proprioceptive sensation was altered over the limbs. On D10 the patient was able to stand up without help, and to walk more than 500 m, but psychomotor slowing was still marked, and he often complained of being disturbed by imaginary flies. On D11 he showed no signs of disorientation or memory trouble, but still complained of blurred vision. On D13 he left the hospital and traveled 5 km on foot to return to his village. The subsequent clinical examinations were performed at home. The hypertonia and the involuntary movements had disappeared on D13. On D20 his face was more expressive, but he still showed marked psychomotor slowing and slowness of voluntary movements. On D27 he was still asthenic and a slight cogwheel phenomenon was found when he performed an important mental effort. Five months after treatment no neurologic abnormalities were found and the patient appeared quite normal, although his relatives stated that his general behavior had changed and that he was much calmer than before treatment.

His pretreatment counts of *L. loa* and *M. perstans* mf/ml were 50,520 and 420 respectively (Table 2). The CSF collected on D4 was clear but contained live *L. loa* mf; they were also found in the blood and urine. The CRP level was

TABLE 2
Biologic results in the five probable cases of *Loa loa* encephalopathy temporally related to ivermectin treatment recorded from 1991 to 1996 in Cameroon*

Patient	Anonymous ^d			Ducorps and others ^e				Case 1	Case 2		Case 3	
Initial <i>Loa loa</i> count†	Very numerous			162,920				?	50,520		152,940	
Initial <i>Mansonella perstans</i> count†	?			198				?	420		100	
Day of examination	D10	D14	D17	D1	D3	D6	D13	D13	D4	D7	D4	D7
Blood <i>Loa loa</i> count†	>1,000			90,520	1,880	790		3,600	1,420	1,780	17,700	9,080
<i>M. perstans</i> count†				66	33	99		960	240	520	180	300
Hemoglobin				14.4	15.2	14.0		16.1	13.8	14.9	12.2	12.4
RBC (10 ⁶ /mm ³)	2.14			3.87	4.77	4.94	4.64	5.42	5.15	5.63	4.12	4.30
Leukocytes (/mm ³)	8,600			11,800	7,300	7,600	6,100	8,000	15,500	17,100	8,500	8,400
Eosinophils (%)	5			1	1.8	7	25	0	15	40	20	0
Platelets (10 ³ /mm ³)				206	143	164		326	280	350	205	233
CPK (IU/liter)					69			207	47		69	165
CRP (mg/liter)					99.7			97.8	62.1	8.8	76.5	9.6
CSF Color	Clear	Clear	Clear	Clear		Clear	Clear	Clear	Clear		Clear	
<i>Loa loa</i> count‡	>100	100	100	0		102	14	10	35		59	
RBC (/mm ³)	57	10	50	<1		4	6	48	14		60	
Leukocytes (/mm ³)	0	4	0	<1		2	4	<1	11		<1	
Glucose (g/liter)	0.90			0.73		0.71	0.66	0.79	0.98		0.66	
Proteins (g/liter)	0.50			0.18		0.51	0.30	0.45	0.41		0.33	
Urine <i>Loa loa</i> count§				+	6	+	+	63	11	6		+
RBC¶				0	+++	++	+	+++	++	4,000		3,000
Leukocytes¶								+++	++	4,000		4,000

* RBC = red blood cells; CPK = creatine phosphokinase; CRP = C-reactive protein.

† Microfilariae per milliliter of blood.

‡ Microfilariae per milliliter of cerebrospinal fluid (CSF).

§ Microfilariae per 5 ml. + = microfilaria present but not counted.

¶ Counts per 5 ml, or evaluated using Multistix[®] reagent strips (Bayer Diagnostics, Tarrytown, NY). RBC: + = 25–80/μl; ++ = 80–200/μl; +++ = ≥ 200/μl. Leukocytes: ++ = 125–500/μl; +++ = ≥ 500/μl.

high on D4 and slightly elevated on D7. The CSF glucose and protein levels were slightly elevated. Hemoglobin electrophoresis indicated that the patient was AS heterozygous. An electroencephalogram (EEG) on D15 showed periodic occurrence, during hyperventilation, of diffuse discharges of large amplitude. On D146, the tracing was asymmetric and characterized by slow activity with additional spikes, indicating focal activities in the right parieto-occipital area, which worsened during hyperventilation. On D233 the abnormalities had disappeared and the tracing did not show any pathologic activity.

Case 3. The patient was 18-year-old schoolboy living in Nkolobang II (4°11'N, 11°19'E) with no notable past medical history, except for left sciatic nerve paralysis due to an intramuscular quinine injection when he was child. The left lower limb was amyotrophic and was not examined subsequently. He complained of joint pains on D1. On D2 he was unable to work and stayed in his bedroom. On the evening of D3 he was found unconscious on his bed, soiled with urine and feces. He was hospitalized on D4, where he lay without voluntary movement either spontaneous or on command. At this time he was incontinent of urine; he opened his eyes and emitted inarticulate sounds in a loud voice, but otherwise did not speak; pain sensation was abolished, the Glasgow coma score was 6, there was no involuntary movement, hypertonia with a marked cogwheel phenomenon was found in the upper limbs, the tendon reflexes of the upper limbs were normal, the patellar reflex was abolished, the Achilles reflex was feeble, and the plantar response was flexor. On D5 and D6 the patient could make voluntary movements of the eyes and head, but he was still incontinent and did not respond to verbal stimulation or to pain; a swinging horizontal movement of the eyeballs was recorded when he had his eyes half-closed, his reaction to pinching was nearly absent, the Glasgow coma score was 9, the tendon reflexes were present, there was no Babinski sign, hypertonia with a cogwheel phenomenon was recorded in the wrists, elbows and knees and no meningeal sign was found. Treatment included perfusion with glucose, tetracosactide, ampicillin, and thiamphenicol. His condition improved considerably on D7; although he remained weak, he could stay seated on the bed when helped, and spoke several sentences; he could perform slow but adjusted voluntary movements, muscular strength and sensation were normal, but the cogwheel phenomenon persisted in both wrists. From D8 to D11 the patient continued to improve; although he was still incontinent, could not stand unaided, and could not say either where he was or what day it was, he recognized the examiners and could correctly answer simple questions about himself; he complained of visual troubles, joint pains and paresthesia of the feet and fingers; the hypertonia had disappeared, but mild motor deficit appeared at the left upper limb on D10. Perfusion was interrupted on D8 but tetracosactide was continued. On D12 the patient could stand up unaided, walk with help and perform simple calculations, and a fundus examination showed bilateral retinal hemorrhages. On D14 he left the hospital, on D15 he could walk unaided, and on D21 there was no deficit of muscular strength, but a mild cogwheel phenomenon persisted at the left wrist. On D47 he went back to school. Five months after treatment, the neu-

rologic examination result was normal but he still complained of headaches and episodic amnesia.

His pretreatment counts of *L. loa* and *M. perstans* mf were 152,940 mf/ml and 100 mf/ml, respectively. The CSF collected on D4 was clear but contained live *L. loa* mf. *Loa loa* mf were also found in the blood and urine. Eosinophilia decreased markedly between D4 and D7. The CRP level was very high on D4 and slightly elevated on D7. The CSF glucose and protein levels were normal. Hemoglobin electrophoresis indicated that the patient was AA homozygous.

The EEG tracing on D19 was slow with spontaneous occurrence of diffuse, paroxysmal, and monomorphic theta activity that lasted 2–3 sec. The slowing of activity was increased by hyperventilation. By D105 an improvement was recorded but focal abnormalities persisted in the left occipital region, especially during hyperventilation. By D159 all previously recorded abnormalities had disappeared.

Patients with serious non-neurologic reactions. The condition of these patients was characterized by functional impairment that required assistance for several days when carrying out their minimal basic everyday activities in the home, such as eating, getting out of bed, getting dressed, or washing themselves. The patients usually stayed in bed or in armchairs, and had difficulty in standing up or walking, even with help. They complained of severe fatigue and diffuse pains. They were not confused, and were able to answer questions, but the replies were slow and slightly delayed. No objective neurologic sign was found and the blood pressure of these patients was normal, but all of them showed mildly elevated temperature on D1 or D2. Pretreatment blood smears were available for 18 of the 20 patients who experienced such conditions. Their geometric mean *Loa* microfilarial load was 83,448 mf/ml.

DISCUSSION

The present paper describes three new cases which meet the definition of PLERI. A total of five cases corresponding to this definition have so far been documented, all of them from Cameroon. That only two cases have been recorded during the carefully monitored incidence study in which 17,877 persons from an area with onchocerciasis, also heavily endemic for *L. loa*, were treated with ivermectin, indicates that such adverse events are rare.¹⁰ However detailed clinical and biologic description of these cases is useful to identify similar cases that could occur during mass IDPs for onchocerciasis in areas of Africa in which loiasis is endemic, and to provide information on their treatment and prognosis.

The clinical and biologic manifestations in five patients with serious neurologic reactions corresponding to the definition of PLERI are summarized in Tables 1 and 2. Several common features should be emphasized. All were young males in apparently good health before treatment. The first symptoms appeared on D1 or D2 after treatment with ivermectin and included fatigue, headache, and joint pains. Disorders of consciousness usually appeared on D3 or D4. In the three nonfatal cases, the symptoms changed rapidly from day to day but the condition was worst on D4 or D5 and then improved progressively to become more or less normal one month after the ivermectin dosage. With regard to clinical signs, the patients were usually incontinent for several

days, the motor deficit was usually mild, but the tendon reflexes were abolished in three cases and brisk in one; no Babinski sign was found, a marked and long-lasting cogwheel phenomenon was present in cases 2 and 3, in whom this sign was sought, and retinal hemorrhages were found in all of the three patients whose fundi were examined (i.e., the case described by Ducorps and others,⁹ and cases 2 and 3 described in the present paper). With regard to biologic results, *L. loa* mf were found in all early examinations of blood, CSF, and urine, but full blood counts did not show any constant pattern in the five cases. In the patients with pretreatment *Loa* microfilaremia greater than 15,000 mf/ml, eosinophilia decreased significantly between D0 and D1, and increased subsequently.⁹ This was not consistent with the results of cases 1 and 3, whose eosinophilias were nil on D12 and D7, respectively. The CRP levels measured were very high when the neurologic signs were maximum. In most cases, red blood cells were found in the CSF, whereas the CSF leukocyte counts were slightly elevated and the glucose and protein levels were normal or only slightly elevated. Red blood cells and leukocytes were also found in the urine but macroscopic hematuria was recorded in only one patient.⁹

Since the description of the first case,⁶ the existence of ivermectin-induced *L. loa* encephalopathy, or PLERI, has been questionable. Two questions have been raised: 1) whether the condition is related to *L. loa*? and 2) whether ivermectin can induce the condition?

With regard to the first question, several points may be made. First, *Loa loa* mf, and not those of any other filarial species, have been found in the CSF of these patients. Their presence there is remarkable finding since no mf of any species has been found in the numerous CSF examinations performed routinely over many years in the Centre Pasteur at Yaounde, which provides this service for the area highly endemic for loiasis from which all five PLERI cases came. Second, a common feature of the five cases is that they all showed exceptionally high *L. loa* microfilaremia, as demonstrated in three cases before treatment and in the two others after treatment. Third, if one assumes that the pathologic process in PLERI is induced by ivermectin, one should remember that this drug, like DEC,^{11,12} has little microfilaricidal effect against *M. perstans*.^{1,13,14} If neurologic manifestations are related to the destruction or death of mf, this may explain why the process develops in patients infected with *L. loa*, and not in those solely infected with *M. perstans*. In addition, the assumption that *M. perstans* can cause neurologic or psychiatric conditions is highly questionable.¹⁵ The only two well-documented cases attributed to *M. perstans* have subsequently been shown to be due to *Meningonema peruzzii*, a filaria of monkeys (Cercopithecidae), a parasite of whose fourth-stage larva has also been found in the CSF of humans.¹⁶⁻¹⁸ Another fourth argument is based on pathologic findings that have shown that in all autopsies of encephalopathic cases involving *L. loa*, the cerebral tissue was diffusely invaded by mf causing microinfarcts and microthromboses.¹⁹⁻²² In contrast, neurologic manifestations attributed to lymphatic filariasis have been recorded on only eight occasions,²³⁻³⁰ and the cerebral lesions involved were generally limited to local granulomata.^{23,25,27,30,31} Finally, an exhaustive search of the literature on neurologic complications

of filarial diseases has been performed to ascertain what species were involved in the various reported cases. This review showed that if one discards all cases of psychoneurotic or purely painful conditions,³²⁻³⁸ most of the remaining cases of objective central neurologic disorders, presumably caused by filariae, have been attributed to *L. loa*.^{19-23,39-59} This difference is all the more striking because the area endemic for *L. loa*, i.e., the rain forest of central Africa, is much more limited than the area endemic for any other filarial species. Infection with *O. volvulus*, has been associated with epileptic seizures but not with motor deficits or encephalopathic conditions.⁶⁰⁻⁶³ The only cases of neurologic complications, six patients with severe vertigo of which one developed an associated quasi-Parkinsonian condition, were reported in patients heavily infected with the Cameroon Sudan-savanna strain of *O. volvulus*, who were treated with DEC following a course of suramin.⁶⁴ However, no similar cases have been reported following ivermectin treatment among the many millions of savanna-dwelling onchocerciasis patients who have been treated since mass IDPs began.

With regard to the assumption that the five PLERI cases documented so far were induced by ivermectin, three arguments may be put forward. First, the initial symptoms began within two days of ivermectin treatment in patients who were previously healthy. Second, ivermectin has been shown to provoke the passage of *L. loa* mf into the CSF.⁹ Third, the fact that microfilaricidal treatment may induce *L. loa* encephalopathy has been clearly demonstrated when DEC was widely used in central Africa. Among all the cases of *L. loa*-related neurologic disorders, most of them, especially the most serious, were related to DEC, whereas those apparently unrelated to previous treatment were exceptions and often questionable with regard to their spontaneous occurrence.⁵²

The fact that all the PLERI cases reported so far came from Cameroon, and especially from the Sanaga Valley, might be due to characteristics of the *L. loa* strains or to human host factors specific for this region. An alternative explanation, which we consider as more probable, is that the mean *Loa* microfilaremia might be higher in the Sanaga Valley than in the other areas endemic for loiasis where ivermectin has been distributed for onchocerciasis. This could be particularly the case in Congo where the distribution programs were carried out principally near Brazzaville, in an area of degraded forest where, although data are scarce, the intensity of *L. loa* infection is presumably low.⁵⁵

Although the induction of *L. loa* encephalopathy by microfilaricidal drugs is now well established, the question remains why some people with high *L. loa* microfilaremia develop such reactions and other do not. Among the 5,550 adults who received their first microfilaricidal treatment and underwent pretreatment blood examination on the occasion of the incidence study, 160 (2.9%) harbored *L. loa* microfilaremia exceeding 30,000 mf/ml, the value that has been proposed as the at risk threshold.⁸ It is possible that cofactors may facilitate the development of *L. loa* encephalopathies after microfilaricidal treatment. It has been suggested that concomitant infections or chronic vascular disease, which make the blood-brain barrier more permeable, may constitute such cofactors.^{19,21,41,65} A priori, there is no evidence that the occurrence of encephalopathy is linked with the

sickle cell gene; although case 2 was AS heterozygous, case 3 was AA homozygous. This observation indicates that the existence of sickle cell trait or sickle cell disease is not a necessary cofactor for the development of PLERI.

Among the five PLERI cases so far recorded, one died following gastrointestinal bleeding⁶ and another died of infectious complications (case 1 in this report). Both of these patients were treated during mass IDPs for onchocerciasis control and the diagnosis of PLERI was established too late for them to be adequately treated in a hospital. Conversely, the three who recovered were treated with ivermectin in the course of clinical studies with careful monitoring, and they were managed in hospital as soon as neurologic manifestations became serious. Early recognition and hospital care appear to be the key to recovery.

Also of importance is the long-term neurologic outlook for patients who survive PLERI, especially since the majority of patients who have survived after spontaneous or DEC-induced *Loa* encephalopathy showed sequelae including motor defects,^{42, 48, 59} extrapyramidal disorders,^{46, 47, 50} ataxia,⁵⁴ disturbances of balance,^{57, 59} aphasia,⁵³ psychomotor slowing,⁵⁰ psychoneurotic disorders,⁵⁷ or dementia.⁵¹ Fortunately, all three patients who survived their PLERI showed no neurologic problems several months after treatment. This progressive clinical improvement was consistent with the progressive disappearance of the EEG abnormalities in cases 2 and 3.

Presently, there is no consensus on the best treatment for patients who develop *L. loa* encephalopathy, especially since there is still uncertainty as to the pathophysiologic mechanisms responsible for the condition. The principles to follow would appear to be early hospitalization, good nursing, maintenance of fluid, electrolyte, and nutritional balance, antihistamines and/or corticosteroids for putative inflammatory lesions in the CNS, and antibiotics to prevent or control possible secondary infections. The two patients in the present series who died had been treated with corticosteroids because of the seriousness of their conditions after several days of coma. However, it is possible that this drug may have contributed to the appearance of the infectious or hemorrhagic complications that led to the fatal outcome. The three patients who recovered were treated with either antihistamines or tetracosactide, but we cannot be certain that this contributed to their recovery.

The means of preventing PLERI require further investigation. This problem is difficult because at the present time during mass IDPs, there is no feasible method of routinely assessing pretreatment mf loads of *L. loa*. However, an interesting finding is that DEC-induced *L. loa* encephalopathy seems to be related to the dose of the drug.⁵⁹ It is possible that doses of ivermectin lower than 150 µg/kg may reduce the risk of neurologic reactions by slowly reducing the *L. loa* microfilaremia below the risk threshold. Subsequent annual doses of ivermectin for onchocerciasis could then be given without risk at the usual dose of 150 µg/kg because the concentrations of *L. loa* do not usually build up to more than 10–15% of their pretreatment levels over the period of a year after treatment.⁶⁶

As can be seen from the results, ivermectin-induced *L. loa* encephalopathies associated with disorders of consciousness are rare. However, in addition to the five cases referred

to here, several patients with high pretreatment *L. loa* microfilaremia developed a serious non-neurologic condition after treatment with ivermectin. This serious condition was defined by the existence of a functional impairment lasting more than one week. For ethical reasons, no lumbar puncture was performed on these patients, but it appears that this post-treatment condition parallels the pretreatment *L. loa* mf load,¹⁰ which suggests in turn that they have a pathologic process in brain tissue similar to, but milder than, that developed by those patients who developed serious neurologic manifestations. Thus, there may be continuum between the mild, marked, and serious non-neurologic cases and those with serious, neurologic conditions. Several cases of serious non-neurologic reactions have been reported in previous observations, but in a brief or anecdotal manner.⁸ The incidence study carried out in the Lekie area¹⁰ has convinced us that reactions of this type, although less serious than PLERI, are nevertheless worrisome in the context of African rural communities and thus should, like the PLERI cases, be recorded early. It should be emphasized that patients who develop such reactions are very weak and require careful medical attention because they are susceptible to life-threatening complications such as dehydration or deterioration of an underlying infection. Those involved in ivermectin distribution programs should be aware that such serious, non-neurologic reactions may occur and that they can be readily managed without hospitalization, but only by ensuring correct rehydration and nourishment. The patient and his family should also be reassured by explaining to them frankly the cause and the transient characteristics of the condition.

The findings reported here suggest several avenues of operational research that could help to reduce the risk of PLERI. 1) More extensive epidemiologic surveys of the distribution of loiasis need to be undertaken to identify populations at risk of PLERI in areas designated for mass IDPs.⁶⁷ 2) Low-cost and practical methods need to be developed to identify individuals in those populations who are at high risk because of their high *Loa* microfilarial load. 3) Specific health educational measures, including information on the risk of serious reactions, and monitoring strategies need to be developed where mass IDPs are organized against onchocerciasis in areas in which loiasis is co-endemic. 4) The effect of ivermectin given at doses less than 150 µg/kg on *O. volvulus* and *L. loa* mf load needs investigation. 5) If and when cases arise, observations on the most appropriate treatment of PLERI should be made.

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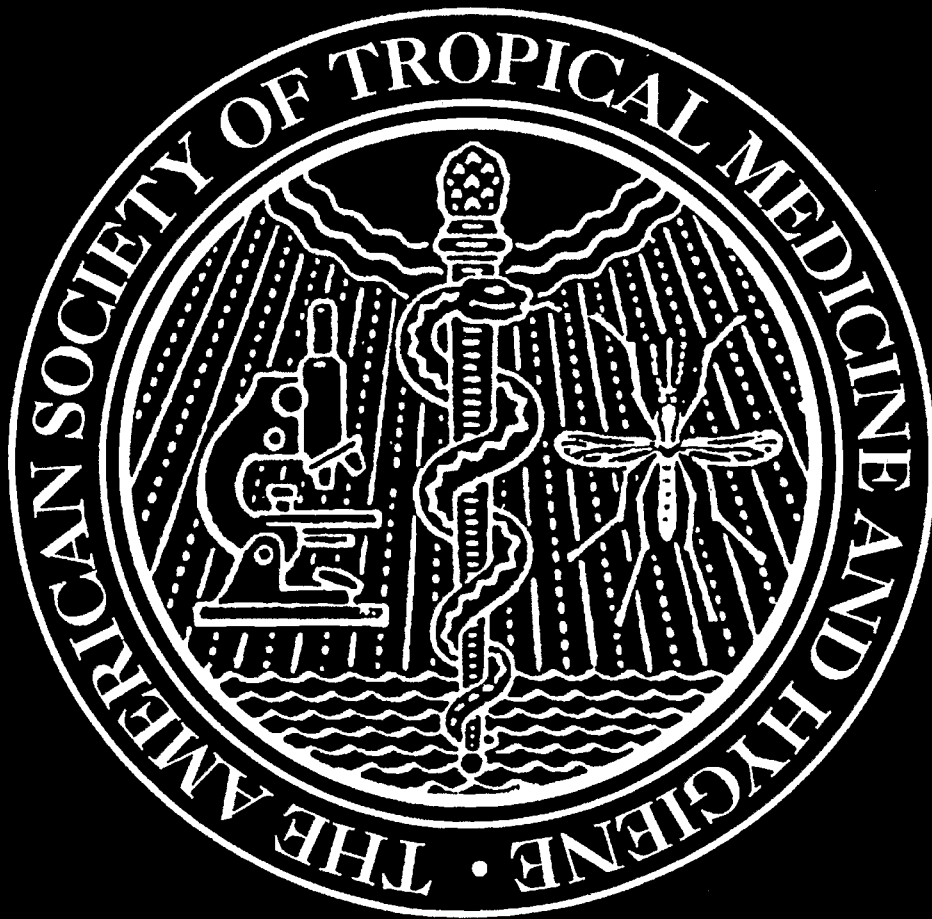
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