Jilek-Aall, Louise
Epilepsy and Onchocerciasis: Pioneering research of Mexican physicians vindicated
Centro Universitario de Ciencias de la Salud
Guadalajara, México

Disponible en: http://www.redalyc.org/articulo.oa?id=14260105
INTRODUCTION: OWN OBSERVATIONS IN EAST AFRICA
While working as physician in the interior of Tanganyika, now Tanzania, East Africa, in the early 1960s, I found an unusual number of patients in the Mahenge mountains of Ulanga District presenting with burns and other injuries contracted during convulsive seizures. In rural Africa, epilepsy is believed to be contagious and caused by witchcraft or evil spirits. Most people are therefore afraid of touching an epileptic person during a seizure. Hence, epileptic persons unfortunate enough to fall into the open domestic fire, are liable to burn themselves without being helped. The epilepsy sufferers are feared and even despised, suffering from terrible burns, often malnourished and depressed, easily succumbing to intercurrent illnesses or dying from their wounds, from drowning, or status epilepticus. When I founded an outpatient clinic for epilepsy in Mahenge in 1960, a stream of patients with severe tonic-clonic epilepsy presented for treatment and within two years the clinic treated hundreds of patients. Preliminary research pointed toward a high family incidence of epilepsy, of a type showing a diversity of neurological pathology not usually observed in epilepsy; such as monoparesis, muscular weakness and atrophy, asymmetric reflexes, mask-like facial expression, drooling from the mouth, monotonous voice and psychomotor retardation (Parkinsonian syndrome), sometimes leading to a cataleptic state lasting for days and usually ending in death. Some patients also showed stunted growth and poorly developed sex characteristics, progressive mental deterioration and/or psychotic episodes (1). The number of epileptic patients rose to over one thousand when I took a Canadian-Tanzanian research team to Mahenge in 1992 to conduct field research, combining epidemiological,
clinical, electroencephalographic and genetic investigations (2). The prevalence of epilepsy was confirmed to be very high and the majority turned out to be focal epilepsies. The usual risk factors for epilepsy in the tropics were present, and family incidence of epilepsy was frequent. But all the well known factors causing a higher prevalence of epilepsy in the tropics could not fully explain the extraordinary high prevalence in the Mahenge region; in some cases more than 100 per 1000 (3). Toward the end of the research project in 1994, I observed that more people with epilepsy also suffered from infection with the filaria parasite *Onchocerca volvulus*, than did people without epilepsy. The mountain region of Mahenge is one of the highest known density areas for endemic onchocerciasis in Tanzania (4). The vector for the parasite in this part of the country is the black fly *Simulium neavei*, which breeds in fast-flowing mountain streams. People in small villages with fields close to such streams were more heavily infested with *Onchocerca volvulus* and had a higher rate of epilepsy than people in the town of Mahenge where there is no stream in the vicinity.

When, at meetings in Limoges, France, 1994 (5) and in London, England, 1995 (6), I presented papers on the possibility that onchocerciasis might provoke epilepsy in predisposed persons, this hypothesis met with scepticism or was rejected outright. The argument was that the microfilariae of *O. volvulus* are only found in the anterior ocular chamber, in the skin and in the lymphatic system; that they, in contrast to microfilariae of other pathogenic filariae, are not found in the blood; and that they are unable to penetrate the blood-brain barrier to damage brain structures. It is well known that in Africa ocular lesions (sclerosing keratitis, iridocyclitis, and optic nerve atrophy) are the most obvious consequences of *O. volvulus* infestation. However, since the optic nerve is anatomically part of the brain, it is conceivable that microfilariae of *O. volvulus* could also damage other parts of the brain and thereby create epileptogenic foci, as well as account for the other neurological symptoms I so often observed in many of my patients. I therefore set out to search the literature for similar observations and studied publications in many languages, also in Spanish.

---

**The Mexican Pioneer Researchers**

I became very interested when I found the work by the Mexican physician Dr. Guillermo Casis Sacre who during the 1930s practiced medicine in the Mexican states of Chiapas and Oaxaca where the filaria parasite *Onchocerca volvulus* is endemic. With his keen clinical observation Casis Sacre noticed that many of the patients with onchocerciasis suffered from epilepsy of a severe type, besides the well known ocular pathology. The first time I examined a patient with onchocerciasis was in 1968 and was very excited about observing a remote village where about 50% of adults suffered from onchocerciasis. From then on the number of recorded observations of multi-organ involvement in onchocerciasis increased, particularly with the spread of the disease in neighboring countries.

In 1957, Casis Sacre published his observations of neurological symptoms in patients with onchocerciasis in the publication *El Sindrome Epileptico y sus relaciones con la Oncocercosis* (The Epilepsy Syndrome and its relationship to Onchocerciasis) (7). His article met with little interest since he had few means to substantiate his clinical findings scientifically. Unfortunately his observations and conclusions were either ignored or dismissed as not scientifically proven. Twenty years later another Mexican investigator, Luis Mazzotti, familiar with the work of Casis Sacre, published an article reporting that he had found dead and also live microfilariae of *O. volvulus* in the blood and in the cerebrospinal fluid of patients with onchocerciasis when they were treated with diethylcarbamazine (Hetrazan) (8). Mazzotti encountered the same scepticism and arguments as Casis Sacre, namely, that microfilariae of *O. volvulus* are not found in the blood, and that in his case also the microfilariae had most probably been introduced into the CSF through contamination of the lumbar puncture needle from the skin. It was only after several decades before researchers began to suspect that onchocerciasis might indeed affect more than skin and eyes.

**Research in Africa during Recent Decades**

Finally from 1970 on, health professionals with African experience began to notice that patients with onchocerciasis manifested a variety of symptoms, including muscle weakness, backache, weight loss and/or failure to grow to normal height (9, 10), they also had a higher than average mortality rate (11). From then on the number of recorded observations of multi-organ involvement in onchocerciasis increased, particularly with the spread of the disease in neighboring countries.

---

*The Mexican Pioneer Researchers*
has increased steadily. Pearson (1985) in his article “¿Are we missing cases of onchocerciasis?”, wrote that musculoskeletal pain in the tropics is frequently the first sign of onchocerciasis and should alert physicians to the diagnosis even before the known skin and eye symptoms occur (12). Nwoke (1992), noticed that people with onchocerciasis frequently suffer from severe backache and called this symptom “parasitic rheumatism” (13). Pearson again wrote another article in 1993 with the telling title “Onchocerciasis is more than skin deep” (14). Burnham, working in Malawi in 1998 stressed the crippling effect of onchocerciasis due to general body aches, backache and joint pain, which in many patients led to a significant lessening of productivity (15).

Why then has it taken so long for medical research in Africa to take up the challenge of the Mexican pioneers’ conclusions that the microfilariae of *Onchocerca volvulus* can damage brain structures and cause the devastating epilepsy syndrome already described by Casis Sacre in 1938? Several reasons account for this. The Mexican research reports lacked sufficient scientific backing, they were published in Spanish in Mexican journals and therefore did not become widely known. The most obvious and well known signs of onchocerciasis, especially in West Africa, have been ocular lesions. The Simulium fly which transmits the parasite to humans, breeds in fast-flowing streams and rivers and infects people who live close to such waters; hence onchocerciasis is known in Africa as “river blindness”. The diagnosis of onchocerciasis is easy to make and does not need invasive procedures, only superficial skin snips, in which the microfilariae of *O.volvulus* can easily be seen under the microscope, the nodules containing the adult worms can be palpated manually. Finally, most of the work on onchocerciasis has been carried out in West Africa where “river blindness” is a more obvious problem than other symptoms of onchocerciasis. Change came when physicians in West Africa involved in the treatment of “river blindness” made the same observation of crucial importance that Mazzotti had made more than 20 years earlier: when onchocerciasis is treated with diethylcarbamazine, microfilariae of *O.volvulus* migrate from the skin through the lymphatic system into the blood vessels; they eventually appear in blood, urine, and in the cerebrospinal fluid (CSF) (16, 17, 18). Duke and co-workers, working in Cameroon 1976, observed neurological complications in some patients during treatment with diethylcarbamazine. This led to an investigation of the CSF before and after treatment (19). They found live microfilariae in the blood and in the cerebrospinal fluid (CSF) already before treatment with diethylcarbamazine was started. Aware of critical comments regarding contamination with microfilariae from the skin when performing lumbar puncture, the first few drops of CSF were collected separately from the main collection. No difference in the microfilaria count was detected in the two samples. Concentration of microfilariae in the CSF during treatment rose a few days later than did the concentration in the blood, indicating a migration from the blood into the CSF as had been suggested by the Mexican researchers. During treatment with diethylcarbamazine, some of the patients suffered from severe vertigo or other neurological complications such as headache, and Parkinsonian symptoms. Most of these complications disappeared a few days into the treatment. On the basis of these findings, Duke and co-workers postulated that live microfilariae of *O. volvulus* in the CSF might gain access to several parts of the brain, such as the pituitary gland, basal ganglia, thalamus and the brain stem, even before treatment with diethylcarbamazine.

Duke’s hypothesis could explain the neurological symptoms found in people with onchocerciasis and epilepsy, corresponding exactly to Casis Sacre’s “epilepsy syndrome”, such as Parkinsonian symptoms, growth retardation, pituitary gland dwarfism, often in combination with retarded sexual development. Even the “head nodding” phenomenon I had observed in the epileptic children of my clinic in Mahenge, Tanzania, which I was told by the parents was an indication that the child will sooner or later suffer from epilepsy (1, 2) could be explained by cerebral lesions due to live microfilariae. This head nodding phenomenon has been observed by clinicians elsewhere in Africa but could not be explained (20, 21, 22).

When in 1987 a new treatment for onchocerciasis was introduced with the semi-synthetic macrocyclic lactone ivermectin (Mectizan) which has fewer side effects than diethylcarbamazine, mass treatment became possible. Kipp and co-workers, while treating onchocerciasis with ivermectin in Uganda, noted that patients who also had epilepsy reported an improvement in their seizure pattern. At first the team thought that perhaps ivermectin itself might have anticonvulsive properties, but found that such an action could not account for the sustained long-term improvement that followed (23). The Ovuga and Kipp team, in a follow-up of seizure improvement after ivermectin treatment, found that the prevalence of convulsive disorders was significantly higher in a village hyperendemic for onchocerciasis than in another village only 10 kilometers away which was hypoendemic for onchocerciasis. This finding paralleled my own observations from Mahenge in Tanzania. Clinical examinations by the Ovuga-Kipp team showed that onchocerciasis was associated with epilepsy as well as with psychological impairment, retarded growth, and retarded sexual development. They came to the same conclusion Duke had already drawn in 1976, namely that it is conceivable that inflammation around live microfilariae in the cerebral cortex could contribute to seizure activity and microfilariae around the pituitary gland could be responsible for the type of dwarfism which is now called Nakalanga syndrome. These researchers therefore also concluded that the association between onchocerciasis and epilepsy is highly likely (24). However, some French researchers performing field studies in West Africa are still casting doubt on the assumption that there is an association between epilepsy and onchocerciasis. Most of their research has involved large numbers of subjects in groups with and without one or the other of the two afflictions, with a combination of both, and with control groups. These field studies have included epidemiological, clinical and laboratory investigations of the highest quality by teams of specialists that cannot be ignored. Probably the best known studies in the last decade were performed by the teams of Kabore 1996 in Burkina Faso (25), Druet-Cabanac 1999 in the Central African Republic (26) and Farrarier 2000 in Mali (27).
None of these research teams reported any statistical evidence supporting the correlation between onchocerciasis and epilepsy. Druet-Cabanac and co-workers concluded that if any cause-effect relation exists, it is not due to the direct effect of microfilariae penetrating into healthy blood vessels and getting into the CSF and the brain; they suggested that other pathophysiologic mechanisms will have to be explored.

**NEW DIRECTIONS IN RESEARCH**

Investigators in West Africa have found that the main pathology of onchocerciasis there is ocular, namely sclerosing keratitis, iridocyclitis and optic nerve atrophy. Investigators in East Africa describe the pathology of onchocerciasis as general malaise, dermatitis, growth retardation, delayed sexual development, and epilepsy, more than ocular disturbances (28, 29, 30). In Sudan (31, 32, 33), Ethiopia (34), and Yemen (35), where onchocerciasis is also endemic in certain areas, inflammatory and atrophic skin lesions, oedema, pigment changes, and a chronic form of papular dermatitis (sowda), are the more prominent symptoms of this filariasis.

The fact that microfilariae of *Onchocerca volvulus* produce different symptoms of onchocerciasis in different geographical regions would seem to indicate that there are differences in the microfilariae themselves. Microfilariae from the different geographical regions were therefore microscopically examined and morphometric measurements carried out by Fischer and co-workers (36). They also cited two works from South America by Schiller et al. (37) and by Yarzabal et al. (38) who had performed similar measurements. It was found that the microfilariae from East Africa as well as those from South America were shorter than those from West Africa. Since the neurological symptoms of onchocerciasis indicating brain damage are very similar in East Africa and in Latin America, whereas the symptoms of onchocerciasis in West Africa appear limited to eyes and skin, Kaiser et al. (39) concluded that the shorter microfilariae of *O. volvulus* in East Africa and South America may have a particular affinity to the central nervous system and may therefore be capable of producing epileptogenic lesions, which the longer microfilariae in West Africa probably may not be capable of.

Other possible pathophysiologic mechanisms have been adduced to explain the connection of epilepsy with onchocerciasis, such as allergic reactions to dying microfilariae, antigen-antibody reactions of the Herxheimer type, strong enough to engender symptoms of encephalopathy which might cause epileptic seizures and other neurological symptoms. These phenomena and the cerebral damage through tropical eosinophilia, apparently precipitated by onchocerciasis in some individuals, are still under investigation and are continually being discussed.

The most recent study in West Africa I could find, was published in 2002 by Boussinesq and his local team (40). It is a report on four years of field research in the central province of Cameroon. Again an attempt was made to clarify whether there is a connection between onchocerciasis and epilepsy. The researchers reasoned that in order to reach a definite conclusion, they had to perform a strictly matched case-control study: the matched epileptic and non-epileptic subjects had to live in the same village, be exposed to the same illnesses, be of the same sex and as far as possible of the same age. They all lived in a region hyperendemic for onchocerciasis where there had been no mass treatment with...
the antifilaria drug ivermectin. The epileptic patients and their matched controls in this study were then investigated for their microfilarial loads. Statistical analysis showed that the microfilarial loads were significantly higher in the epileptic group than in the control group. The Boussinesq team concluded that their research data strongly support the existence of a causal link between epilepsy and onchocerciasis.

Conclusion
In this paper I discussed the possibility that onchocerciasis may explain why epilepsy occurs with very high prevalence in certain tropical areas. The question has not been fully answered whether microfilariae of *Onchocerca volvulus* can penetrate the blood-brain barrier and thereby cause cerebral lesions leading to convulsive seizures and other neurological and endocrine symptoms, as already described by Casis Sacre as “epileptic syndrome” in 1938. However, an increasing number of researchers have in recent years found conditions corresponding to this syndrome in areas of high endemicity of onchocerciasis. Unequivocal evidence of a causal connection could be obtained by direct examination of brain material, but autopsies have not been possible during the field studies hitherto conducted among rural populations in the tropics; non-invasive investigations would be needed. The few electro-encephalographic studies hitherto made in the field of epileptic patients infected with *Onchocerca volvulus*, demonstrated in the great majority of cases multifocal EEG patterns compatible with multiple cerebral lesions (2, 21). Modern imaging methods would go a long way to determine whether the microfilariae of *Onchocerca volvulus* are capable of causing focal cerebral lesions leading to epileptic seizures and other neurological symptoms. Should this indeed be demonstrated, then the eradication of this filaria parasite would eliminate the many ailments caused by onchocerciasis and reduce the prevalence of epilepsy which remains one of the most physically, mentally and socially disabling afflictions in tropical regions (41). The Mexican researchers Casis Sacre and Mazzotti, who were the first to provide data suggesting an association between onchocerciasis and epilepsy, should finally receive the recognition they deserve.

Epilogue
In deference to Casis Sacre, I wish to quote a passage from the article he wrote after years of field work in rural Mexico during the 1930s (7). His two rules are to be remembered the way they deserve.

Recordaremos dos reglas clínicas que deben servir de guía en la ciencia diagnóstica: 1a. Cuando se interroga a un enfermo, lo que no se sospecha no se busca; lo que no se busca no se encuentra; 2a. Durante el interrogatorio de un enfermo no se llevará ningún prejuicio para llegar al diagnóstico de su padecimiento porque entonces los datos obtenidos encajan o se hacen encajar en el diagnóstico que se ha formulado de antemano (Casis Sacre 1938: 15).

Referencias Bibliográficas