

Gaps in Our Understanding of Onchocerciasis-Associated Epilepsy

Session Date: Saturday, October 27

Session Time: 9:00am – 12:00pm

Session Location: St. Jerome, 3rd Floor

Session Description: There has been increasing interest in an epidemiological association between onchocerciasis and epilepsy. Some studies have found an association with the presence of infection, others have failed to find one with the presence of infection but have found an association with higher *Onchocerca volvulus* microfilarial load, and still others have failed to find any association. The picture is further clouded by Nodding syndrome, an apparently epidemic illness localized in certain areas in sub-Saharan Africa; and Nakalanga syndrome, a developmental disorder that sometimes results in epilepsy. Recent data have also demonstrated antibody cross-reactivity between tropomyosin in *O. volvulus* and leiomodins-1, an epitope expressed in several human tissues.

This symposium will review Nodding syndrome and Nakalanga syndrome, data on cross-reactive antibodies, and the epidemiologic cases for and against an association between onchocerciasis and epilepsy. The discussion will focus on identifying the gaps in our understanding and methods for filling those gaps.

Session Chairs: **James J. Sejvar**, Division of High-Consequence Pathogens and Pathology and Division of Vector-Borne Infectious Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention
Paul T. Cantey, Onchocerciasis Elimination and Scabies Control, World Health Organization

Session Rapporteur: Charles Mackenzie

KEY DISCUSSION POINTS

- Data are mixed about the association between onchocerciasis and epilepsy. Epidemiologic associations have been identified in a variety of studies (e.g., observational, case-control, meta-analyses, pooled analysis) and one retrospective cohort study identified a dose-response. Concerns about the results include lack of a standard assessment for both onchocerciasis and epilepsy and the lack of systematic assessment for potential confounders.
- There is stronger evidence for a causal relationship between onchocerciasis and Nodding Syndrome. An auto-immune response to leiomodins-1, due to cross-reaction with onchocercal epitopes, is a viable hypothesis, though more work is needed to demonstrate causality.

- Consensus was reached that determining causality was not important if currently available strategies for the acceleration of onchocerciasis transmission were to be recommended (e.g., twice per year ivermectin mass drug administration) as achieving the interruption goal is important regardless of whether it also prevents epilepsy or Nodding Syndrome.
- Consensus was also reached that determining causality for epilepsy and/or Nodding Syndrome was important if new strategies to prevent development of either diseases were needed, as investments would need to be made to generate the needed efficacy and safety data.

Note: There was little discussion about Nakalanga syndrome, and the epidemiological studies reviewed examined the relationship between onchocerciasis and epilepsy but not Nodding Syndrome.

KNOWLEDGE GAPS IDENTIFIED

- A causal role of onchocerciasis in the development of epilepsy or Nodding Syndrome has not been demonstrated.
- The efficacy of once-per-year and twice-per-year ivermectin on reducing the incidence of epilepsy or Nodding Syndrome in areas with hyperendemic onchocerciasis has not been demonstrated. This should be done to determine if currently available tools might reduce the incidence of epilepsy.
- A systematic assessment of potential confounders of the relationship between onchocerciasis and epilepsy should be developed.

RECOMMENDED NEXT STEPS

- Much of the evidence supporting an association between onchocerciasis and epilepsy is derived from weak epidemiological data. **Stronger data** from a prospective cohort study would provide stronger evidence. **Better use of standardized diagnosis** of onchocerciasis and epilepsy and more systematic evaluation for potential confounders is needed.
- **Better delineation of the pathophysiological pathway** for the development of Nodding Syndrome and the role of onchocerciasis in this pathway would be important in order to direct appropriate development of novel prevention strategies.
- A study **comparing the impact of ivermectin treatment once per year and twice per year on the incidence of epilepsy** in areas with high prevalence of both epilepsy and onchocerciasis could provide evidence to both support a causal role of onchocerciasis and to demonstrate efficacy ivermectin as it is currently used.