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Impact of Mass Treatment of Onchocerciasis with Ivermectin on the Transmission of Infection

HUGH R. TAYLOR,* MICHEL PACQUÉ, BEATRIZ MUÑOZ, BRUCE M. GREENE

Onchocerciasis is a major blinding disease that, until recently, has been essentially untreatable. Ivermectin is a safe and effective drug for the mass treatment of onchocerciasis and when used on an individual basis, it reduces the ability of the treated person to transmit *Onchocerca volvulus* infection. In the present study, the effect of community-based ivermectin treatment on the degree of transmission within the community was assessed by determining the incidence of new infection in children. Ivermectin was distributed annually on three occasions to the eligible members of a population of approximately 14,000 people living on a rubber plantation in a forest area endemic for onchocerciasis. After 2 years, the prevalence of infection in 5-year-old children decreased by 21%. The annual incidence in an uninfected cohort of children decreased by 35% and, after age-specific adjustment, the reduction in incidence in 7- to 12-year-old children was 45%. Thus, community-based distribution of ivermectin led to a significant reduction in incidence of new infection. These findings suggest that ivermectin can be important in reducing the transmission of onchocerciasis.

APPROXIMATELY 85 MILLION PEOple live in areas endemic for onchocerciasis, and 18 million people are infected with *Onchocerca volvulus* (*1*). Onchocerciasis causes blindness or visual loss in 1 to 2 million of these infected people. More than half of the inhabitants of hyperendemic areas will become blind before death, and life expectancy of those who are blind is one-third that of their sighted peers (*2*).

Onchocerciasis is caused by the filarial parasite *O. volvulus*. In nature, humans are the only known reservoir. Adult worms, found in tissue nodules, produce millions of microfilariae that migrate throughout the body, concentrating particularly in the skin and eye. This infection is transmitted by black flies of the simulium species and has a prepatent period of 9 to 15 months (*1*). Adult worms may live up to 18 years in the human host.

H. R. Taylor, M. Pacqué, B. Muñoz, Dana Center for Preventive Ophthalmology, The Wilmer Ophthalmologic Institute, Johns Hopkins University, Baltimore, MD 21205.
B. M. Greene, The Division of Geographic Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294.

*To whom correspondence should be addressed.

Ivermectin is effective against a wide range of parasites (*3*) and is an effective and well-tolerated drug for individual treatment of onchocerciasis (*4–7*). It promises to revolutionize treatment of onchocerciasis by making feasible large-scale community-based treatment (*8, 9*). Ivermectin also may decrease the ability of infected individuals to contribute to transmission (*10*) and lead to a decrease in vectorial transmission (*11, 12*). However, given the efficiency of the simulium vectors and the high transmission capacity in endemic areas, it is unclear whether the effect of ivermectin seen in individuals would be seen with community-based treatment or whether it would be of programmatic importance. The following study tested whether treating a large population with ivermectin would decrease transmission sufficiently to reduce the incidence of new infection.

This study was conducted between September 1987 and November 1989 at the Liberian Agricultural Company (LAC) rubber plantation where approximately 14,000 people live (*8*). Prevalence of infection there increases with age, ranging from 26% at age 5 to 86% at 20 years (*8*). All persons over 12 years of age were eligible for treatment with

ivermectin (150 μg per kilogram of body weight), except pregnant and lactating women, children under 5 years of age, those aged 5 to 12 years who had negative skin snips, and the seriously ill (*8*). Children were treated only after their skin snip status was known and they had been positively reidentified in a polaroid photograph. The study protocol was reviewed and approved by Johns Hopkins University School of Medicine, the Liberian Institute for Biomedical Research, and the World Health Organization (WHO).

The total population was 13,704 in 1987; 13,977 in 1988; and 14,110 in 1989. In 1987 and 1988, 56% and 58% of the population, respectively, were eligible for treatment and 97% of these actually received treatment.

All inhabitants of five sample camps had skin snips taken before treatment in 1987, 1988, and 1989. After treatment, both prevalence and density of microfilariae in the skin were significantly reduced. The geometric mean of microfilariae counts in treated infected people fell from 4.96 microfilariae per milligram (mf/mg) of skin before treatment to 0.81 mf/mg skin in 1989 (84% reduction; paired t test 13.3, $P < 0.001$), and overall microfilarial load for all inhabitants fell from 2.20 mf/mg before intervention to 0.77 mf/mg in 1989 (65% reduction; t test 11.3, $P < 0.001$). Overall prevalence of positive skin snips in adults fell from 88% before treatment to 67% 2 years later (24% reduction; χ^2_2 44.7, $P < 0.001$).

Changes in incidence of infection in children were estimated in several ways. First, the overall incidence of infection was assessed in a cohort of children with negative skin snips (Table 1). Baseline incidence of infection determined in 1988 was 14.9%; incidence in 1989 was 9.7%. Reduction in incidence of new infection in children with negative skin snips was 35% ($\chi^2 = 12.3$, $P < 0.001$).

Second, as incidence of new infection varied with age, the age-adjusted incidence in children aged 7 to 12 years in 1988 (16.4%) was compared with incidence in children of the same age group in 1989 (9.1%) (Table 1). Reduction in age-adjusted incidence was 44.5% ($\chi^2 = 12.6$, $P < 0.001$).

Finally, it should follow that a reduction in transmission would lead to a reduction in prevalence of infection in young children. The mean baseline prevalence of infection in 5-year-old children was 23.9% (Table 2) and had fallen to 19% in 1989, a reduction of 21% ($\chi^2 = 4.13$, $P = 0.04$). The reduction in prevalence was even greater in those 5-year-olds who had lived on the plantation 1 year or more compared to those who recently moved to LAC (35%, $\chi^2_1 = 5.05$, $P = 0.02$) (Table 3). Those who had lived continuously on the plantation would have had a greater opportunity to benefit from the impact of ivermectin treatment than those who had recently arrived, most coming from areas with uncontrolled transmission.

The reduction in transmission that was detected results largely from the initial round of treatment. This is because the prepatent period for *O. volvulus* infection is approximately 1 year (*1*), and there is, therefore, a lag period of 1 year before the impact of treatment can be detected. Given this, one would expect a progressive reduction in transmission commensurate with progressive reduction in both microfilarial densities and prevalence with further annual rounds of repeated treatment.

Previous studies have shown that after individual treatment with ivermectin the number of microfilariae taken up by black flies is reduced considerably (*10*) and community-based treatment may lead to reduction in vectorial transmission potential (*11, 12*). Here we found that community-based distribution of ivermectin had a measurable impact on incidence of new cases of infection, which indicates a reduction in transmission.

Table 2. Prevalence of positive skin snips in all children 5 years old.

Year	Total	Positive	Prevalence (%)
1987	396	94	23.7
1988	452	109	24.1
1989	480	91	19.0

Table 3. Prevalence of positive skin snips in 1989 in 5-year-olds who had lived at LAC for 1 year or more compared to immigrants. Immigrants were children who had moved to LAC since the last distribution of ivermectin treatment and had lived on LAC for less than 1 year.

Migration status	No. of children	Positive	Prevalence (%)	Reduction (%)
Residents	327	53	16.2	35
Immigrants	153	38	24.8	

*$\chi^2 = 5.05$; $P = 0.02$.

Table 1. Incidence of infection in the 1987 cohort of children with negative skin snips. Before treatment distribution in 1987, skin snips were taken from 2371 children aged 5 to 11 years. In 1988, those children who had been skin snip negative together with children who had reached age 5 had skin snips taken. In 1989, skin snips were taken from those children who had remained negative in 1988, together with the children who were now aged 5 years. Age was determined by birth certificate or hospital registration card where available or by reference to a specially constructed local events calendar. Skin snips were taken from the calf of each leg and each iliac crest with a 2-mm sclerocorneal punch. Skin snips were handled in a standardized way and microfilariae were counted under an inverted microscope (*5*). We have expressed the microfilarial load as microfilariae per milligram of skin using the geometric mean of four snips per person.

Age	1987			1988			1989			
	No. snipped	No. positive	Prevalence (%)	No. snipped	No. positive	Incidence (%)	No. snipped	No. newly positive	Incidence (%)	Incidence reduction (%)
5	396	94	23.7							
6	355	106	29.9	189	17	8.9				
7	388	140	36.1	178	35	19.7	105	8	7.6	61
8	317	134	42.3	176	22	12.5	101	6	5.9	53
9	334	162	48.5	116	14	12.5	106	10	9.4	25
10	300	164	54.7	112	19	17.0	72	6	8.3	51
11	281	171	60.9	90	13	14.4	53	4	7.6	47
12				70	19	27.1	44	10	22.7	16
13							35	6	17.1	
Overall incidence				931	139	14.9	516	50	9.7	35*
Age-adjusted incidence (7- to 12-year-olds)				742	122	16.4	481	44	9.1	45**

*$\chi^2_1 = 12.3$; $P < 0.001$. **$\chi^2_1 = 12.6$; $P < 0.001$.

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Extrageniculate Vision in Hemianopic Humans: Saccade Inhibition by Signals in the Blind Field

R. RAFAL,* J. SMITH, J. KRANTZ, A. COHEN, C. BRENNAN

The functional competence of extrageniculate visual pathways in hemianopic humans was demonstrated by showing that distractor signals in the blind half of the visual field could inhibit saccades toward targets in the intact visual field. This inhibitory effect of unseen distractors in patients occurred only when distractors were presented in the temporal half of the visual field, was specific to oculomotor responses, and did not occur in normal subjects. These results show that a peripheral visual signal activates retinotectal pathways to prime the oculomotor system and that these pathways can mediate orienting behavior in hemianopic humans.

THE ENCEPHALIZATION OF VISUAL function in the cerebral cortex is a relatively new development in phylogeny. The geniculostriate pathway is fully developed only in mammals. The dominance of this pathway in human vision over the older retinotectal pathway to the midbrain is striking in neurologic patients who have suffered complete unilateral destruction of the striate cortex or its geniculostriate afferents. They are blind in the half of the visual field contralateral to the lesion and cannot see even salient signals within the scotoma (blind area).

However, some visual processing may be preserved in the hemianopic field. Researchers have demonstrated this "blindsight" by requiring hemianopic subjects to move their eyes or reach toward signals that they cannot "see" and by using forced-choice discrimination tasks (*1*). Although light-scatter artifact (*2*) has been excluded as the cause for at least some of these effects (*3*), the physiologic mechanisms of blindsight remain uncertain. In some patients, residual vision may be mediated by spared geniculostriate fibers and could reflect degraded cortical vision near the perceptual threshold (*4*). On the other hand, some blindsight phenomena may reflect processing of visual input from retinotectal afferents to the superior colliculus (*5*). The current investigation shows that signals in the hemianopic field activate the oculomotor system and that retinotectal pathways can mediate orienting behavior in hemianopic humans.

As a test of extrageniculate mediation, we exploited a lateralized neuroanatomic arrangement of retinotectal pathways that distinguishes them from those of the geniculostriate system. When compared to the geniculostriate system, the retinotectal pathway has more crossed fibers from the contralateral eye, and the temporal hemiretina (nasal hemifield) has a smaller direct input to the superior colliculus. In cats, this pathway is almost entirely monocular (*6*), and cats with bilateral occipital ablations in which extrageniculate vision is restored by intercollicular section orient only toward signals in the temporal hemifield (*7*). In monkeys, this anatomic asymmetry is much less complete (*8*). Nevertheless, the functional relevance of this anatomic asymmetry in humans was shown by demonstrating that newborns (in whom the geniculostriate pathways are not developed) have a strong bias to saccade to signals in the temporal hemifield (*9*). Even in adults, the bias to saccade toward the temporal hemifield persists under conditions of bilateral, simultaneous stimulation

Table 1. Median saccade latency in milliseconds for each patient. Data are expressed as median ± SEM.

Patient	Distractor-target interval (ms)				
	−500	0	50	150	250
			Temporal distractor		
1	326 ± 25	372 ± 18	360 ± 17	265 ± 18	273 ± 14
2	368 ± 28	415 ± 23	395 ± 19	239 ± 19	328 ± 35
3	268 ± 11	291 ± 12	269 ± 8	264 ± 11	265 ± 12
			Nasal distractor		
1	299 ± 14	282 ± 11	291 ± 14	243 ± 16	258 ± 18
2	358 ± 20	324 ± 14	357 ± 15	316 ± 25	321 ± 37
3	278 ± 8	276 ± 11	256 ± 10	284 ± 12	278 ± 9

Table 2. Mean reaction time in milliseconds for the hemianopic patients in the key press task. Data are expressed as mean ± SEM.

Distractor-target interval (ms)				
−500	0	50	150	250
		Temporal distractor		
458 ± 64	413 ± 60	403 ± 62	381 ± 28	418 ± 46
		Nasal distractor		
448 ± 66	446 ± 66	377 ± 46	372 ± 69	376 ± 68

R. Rafal, J. Smith, J. Krantz, Department of Clinical Neurosciences, Brown University, Providence, RI 02908.
A. Cohen, Department of Psychology, Indiana University, Bloomington, IN 47405.
C. Brennan, Cornell University School of Medicine, New York, NY 10021.

*Current address: Department of Neurology, University of California, Davis, and Martinez Veterans Administration Medical Center, 150 Muir Road, Martinez, CA 94553.