SYMPTOMS REPORTED AFTER MASS DRUG ADMINISTRATION FOR LYMPHATIC FILARIASIS IN LEOGANE, HAITI

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INTRODUCTION

Approximately 120 million people worldwide are affected by lymphatic filariasis (LF). In Haiti, 8 million people are at risk, and > 600,000 are infected with the parasite *Wuchereria bancrofti*.1–3 One endemic area of Haiti is the Leogane Commune, which is located ~30 km west of the capital, Port au Prince. The filariasis program started there in 2000, and since that time, between 55,000 and 102,000 people have been treated annually with anti-filarial mass drug administration (MDA).4,5 By treating the entire at-risk community, the program aims to decrease the prevalence and density of circulating microfilaria (MF) and thereby to interrupt transmission.6–12 The medications used in Leogane are diethylcarbamazine (DEC) and albendazole.

The MDA may result in systemic adverse reactions from the death of circulating MF. These systemic symptoms, which occur in 5–100% of treated individuals, include fever, dizziness, headache, pruritus, and myalgias.13–17 The number of persons experiencing these reactions seems to correlate with the prevalence of microfilaremia in the community and the severity of the reaction to correlate with the density of the infection.14,15,18–20 Adult worm death can result in scrotal nodules.19,21

Although the frequency of adverse reactions is generally less than the prevalence of infection in the community, this has not been the case in Leogane. Microfilaremia has decreased from 73% to 100% at the four sentinel sites from 2000 to 2003, whereas reported symptoms of adverse reactions in the whole of Leogane Commune have persisted out of proportion to the prevalence of infection.4 From 2000 to 2003, the number of symptoms was substantially more than the expected number based on sentinel site MF prevalence.4 In this study, we evaluated a cohort of persons reporting symptoms after the 2004 MDA to determine whether symptoms were associated with filarial infection and to explore the grammatical necessity of surveillance and free treatment of symptoms.

MATERIALS AND METHODS

The fifth MDA occurred from October 7 to 10, 2004 in Leogane, Haiti. Distribution occurred at 148 posts located in health clinics, churches, schools, and private houses. Participants received 400 mg albendazole and weight-based dosing (6 mg/kg) of DEC up to a maximum of 400 mg. Pregnant women and children < 2 years of age did not receive DEC or albendazole.4 Numbers of MDA participants were tallied daily by program volunteers.

As in previous years, program volunteers at the posts told MDA participants to return to the same post if they required treatment of symptoms experienced after the MDA.22 This free symptomatic treatment of minor symptoms included antibiotic for abdominal pain, oral rehydration solution for vomiting or diarrhea, paracetamol or ibuprofen for headache, paracetamol for fever, and promethazine for pruritus. Participants usually received several doses of medication (enough to provide treatment for ~24 hours). They could return more than one time to the health post, but those with more serious symptoms were referred to the local hospital, Hospital Sainte Croix. After the MDA ended, participants with any symptom requiring treatment were told to go to the hospital and not the distribution post.

Persons seeking treatment at distribution posts. For this cross-sectional evaluation, 5 distribution posts were selected from among those 20 that had the highest number of MDA participants in 2003 and were easily accessible. All persons returning to the five selected sites with self-reported symptoms during the 4 days of the MDA were asked to participate. If they developed symptoms between 4 and 7 days after the start of the MDA, they were interviewed at Hospital Sainte Croix. After obtaining verbal consent, trained nurses administered standardized questionnaires using Dell Axim handheld computers (Dell, Round Rock, TX) programmed with Visual CE software (SYWARE, Cambridge, MA). Participants were asked about demographic characteristics, current symptoms, participation in prior MDAs, and symptoms experienced after MDAs in previous years.
Men seeking treatment at hospital. Because scrotal symptoms occurred less frequently than systemic symptoms after previous MDAs, this part of the study was not limited to the five selected sites. Men from any of the distribution posts in Leogane, who reported post-MDA scrotal pain, were told to go to Hospital Sainte Croix. There, the same standardized questionnaire was administered, and a physician or nurse performed a scrotal examination to document the presence of nodules.

Ethics. The program evaluation was carried out under an institutional review board protocol previously approved by the Centers for Disease Control and Prevention. Informed consent was obtained from all adult participants and from parents or legal guardians of minors.

Antigen testing. Immunochromatographic testing (ICT) was performed using 100 µL of capillary fingerstick blood obtained from those with systemic and scrotal symptoms. This rapid-format card test detects circulating *W. bancrofti* adult worm antigens (Binax ICT, Portland, ME). After 10 minutes, results are read as positive (infected) or negative (uninfected). The test has a sensitivity of 65–100% (96–100% for those who are MF positive and 65–100% for those who are infected based on serologic testing but are microfilaremic) and a specificity of 94–100%.23

Statistical analysis. Univariate and stratified statistical analysis was performed using SAS version 9.1 software (SAS Institute, Cary, NC). *P* values were calculated using the two-tailed Fisher exact test for binary variables. A logistic regression model assessed the association between independent variables (age, sex, and ICT status) and events, with events classified as the proportion of previous MDAs that resulted in symptoms (years in which symptoms occurred after the MDA/number of previous MDAs). The number of years in which symptoms were reported and the number of previous MDAs were both count variables (range, 1–4). Age was categorized by decade starting with ages 2–10. The Hosmer and Lemeshow goodness-of-fit test produced a *P* value of 0.18. A nonparametric trend was performed to look for an association between age and ICT result; age was again included as a categorized value in 10-year age groups starting with ages 2–10.

RESULTS

Persons seeking treatment at distribution posts. A total of 121,715 persons participated in the 2004 MDA in Leogane Commune, Haiti, and 3,827 (3.1%) returned to the distribution posts seeking treatment of symptoms after the MDA. At the five selected sites, 3,781 persons took part in the MDA; of these, 314 persons (8.3%) returned reporting symptoms. Of these, 170 (54.1%) were women, and the median age was 24.5 years. The majority of respondents (59.9%) developed symptoms < 24 hours after the MDA (Table 1, for ICT-tested individuals only). No one in the study required hospitalization.

The 314 persons interviewed reported between 1 and 4 current symptoms with a mean of 1.5. Of these, 150 (48%) reported that the symptoms interfered substantially with their daily activities. The most commonly reported conditions were headache (36%), gastrointestinal complaints (28%), and dizziness (27%). Less commonly reported symptoms were fever (23%), myalgias (21%), pruritus (7%), and scrotal pain (11% of men). Symptoms reported by < 1% of respondents were leg pain/swelling (three people); breast pain/swelling (three); neck pain (two); and anorexia, fatigue, increased salivation, a bump on the leg, puffy cheeks, and tachycardia (one each).

Of the 314 persons with symptoms after the MDA, 294 (94%) consented to the ICT. Of these, 47 (16%) were antigen-positive (Table 1). Among the respondents, a positive ICT result was associated with increasing age (as a categorized variable in 10-year increments; *χ*² test for trend, *P* < 0.001; Figure 1). Antigenemia was not associated with sex (*P* = 0.11). The majority of persons with any one particular symptom were ICT negative. For example, only 15% of those

### Table 1

Characteristics of persons with systemic symptoms, classified by ICT results, Leogane, Haiti, 2004 (*N* = 294)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No.</th>
<th>ICT positive [N (%)]</th>
<th>ICT negative [N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>47</td>
<td>16 (34%)</td>
<td>247 (84%)</td>
</tr>
<tr>
<td>Median age (yr)</td>
<td>27</td>
<td>21 (78%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Range</td>
<td>5–69</td>
<td>5–69</td>
<td>5–69</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>20 (74%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>7 (35%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Mean no. previous MDAs</td>
<td>2.3</td>
<td>2.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Range</td>
<td>0–4</td>
<td>0–4</td>
<td>0–4</td>
</tr>
<tr>
<td>Mean no. previous years with symptoms</td>
<td>1.1</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–4</td>
<td>0–4</td>
<td>0–4</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache (N = 102)</td>
<td>15</td>
<td>(14.7%)</td>
<td>87 (85.3%)</td>
</tr>
<tr>
<td>Gastrointestinal (N = 83)</td>
<td>9</td>
<td>(10.8%)</td>
<td>74 (89.2%)</td>
</tr>
<tr>
<td>Dizziness (N = 83)</td>
<td>13</td>
<td>(15.7%)</td>
<td>70 (84.3%)</td>
</tr>
<tr>
<td>Fever (N = 67)</td>
<td>11</td>
<td>(16.4%)</td>
<td>56 (83.6%)</td>
</tr>
<tr>
<td>Myalgias (N = 64)</td>
<td>12</td>
<td>(18.8%)</td>
<td>52 (81.2%)</td>
</tr>
<tr>
<td>Pruritis (N = 22)</td>
<td>4</td>
<td>(18.2%)</td>
<td>18 (81.8%)</td>
</tr>
<tr>
<td>Scrotal pain (N = 14)</td>
<td>5</td>
<td>(35.7%)</td>
<td>9 (64.3%)</td>
</tr>
<tr>
<td>Other (N = 13)</td>
<td>1</td>
<td>(7.7%)</td>
<td>12 (92.3%)</td>
</tr>
<tr>
<td>Interval between MDA and symptom onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 day (N = 169)</td>
<td>29</td>
<td>(17.2%)</td>
<td>140 (82.8%)</td>
</tr>
<tr>
<td>1–&lt; 2 days (N = 70)</td>
<td>8</td>
<td>(11.4%)</td>
<td>62 (88.6%)</td>
</tr>
<tr>
<td>2–&lt; 3 days (N = 40)</td>
<td>7</td>
<td>(17.5%)</td>
<td>33 (82.5%)</td>
</tr>
<tr>
<td>≥ 3 days (N = 10)</td>
<td>5</td>
<td>(50.0%)</td>
<td>7 (50.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

### Figure 1

Percentage of symptomatic persons within each age group who have positive ICT results, Leogane, Haiti, 2004 (*N* = 294).
with headache and only 16% of those with fever were ICT positive (Table 1).

Of the 307 individuals who reported whether they had participated in previous Leogane MDAs, the largest proportion (44%) reported participating in all four prior MDAs (mean = 2.6). The mean number of times participants experienced post-MDA symptoms was 1.3 (median = 1.0). Sex was not associated with increased frequency of prior symptoms ($P = 0.86$). Increasing age, however, was associated with an increased likelihood of previous MDAs resulting in symptoms, even when controlling for both sex and current ICT status ($P < 0.001$). Of the 44 persons who participated in all five MDAs and reported symptoms after every MDA, 39 (88.6%) were ICT negative when tested after the final MDA.

**Men seeking treatment at hospital.** Eighty-one men who had participated in the MDA at any of the sites in Leogane Commune went to the hospital complaining of scrotal pain. Of these, two had first gone to the distribution post and were also included in the analysis of systemic symptoms above. More than one third of the men (38.8%) had no nodules on exam, whereas the remaining 42 (53.2%) had at least one nodule (40 had one nodule, 2 had two nodules). Of the 69 men who consented to ICT testing, 18 (26.1%) were ICT positive. Of the 31 men found to have no nodules on exam, 4 (12.9%) tested positive for ICT compared with 14 (37.8%) of the 37 men who had one or more nodules ($P = 0.03$; Table 2).

**Attitudes toward treatment of people seeking care.** The majority of people visiting distribution posts and those who returned to the hospital did not cite post-MDA symptoms as a deterrence to participating in future MDAs. When asked, “If side effect medications were not available, would you participate in future MDAs?,” 82% of those with systemic symptoms and 78% of those with scrotal symptoms said yes. When asked “Would you pay for side effect medications?,” 73% of those with systemic symptoms and 72% of those with scrotal symptoms said yes.

**DISCUSSION**

Given limited resources, LF programs are faced with the question of how to minimize costs. Monitoring and treating post-MDA symptoms can present a significant financial and administrative challenge, and the value of doing so has not been evaluated. This cross-sectional study sought to answer the question as to whether persons who reported symptoms after the fifth annual MDA had evidence of filarial infection and whether continued active surveillance for, and free treatment of, post-MDA symptoms remains necessary. We showed that the majority of persons reporting systemic and scrotal symptoms after the 2004 MDA in Leogane, Haiti, had no detectable filarial infection at that time. From a programmatic perspective, treatment of such symptoms may not be necessary, because most persons surveyed did not report symptoms as a barrier to participating in future MDAs.

Although pre-MDA MF testing by microscopic examination (not ICT) would have been the ideal way to determine if systemic symptoms were from parasite death, ICT sensitivity is 96–100% in those with circulating MF. Given that very few of those with systemic symptoms had positive ICT results at the time, most symptoms reported after the 2004 MDA were unlikely to have been caused by MDA-induced MF death. This was the case even for those reporting symptoms that have been previously described as resulting from MF death. Among the men who reported scrotal pain in our study, the low percentage of ICT positivity and nodules on examination suggests that not all of these men had filarial infection. Men who had nodules detected on physical exam were more likely than those without nodules to have evidence of infection based on ICT testing.

The ICT results suggest that most reported systemic and some scrotal symptoms may be caused by unrelated medical conditions and health care–seeking behavior of the participants. This hypothesis is supported by our finding that older subjects (who may be more likely to have chronic medical conditions) were symptomatic more frequently in the past—regardless of their antigen status at the time of the study. The fact that older participants were more likely to be antigenic is not unexpected, given they had a longer period of exposure. Reported symptoms may also reflect raised expectations of free medication after years of intensive education, monitoring, and treatment of adverse reactions in Leogane. Despite this health care–seeking behavior, participants stated their willingness to engage in future MDAs (even without symptomatic treatment) and pay for any needed medications. Given the low doses of DEC and albendazole used in the MDA, it is less likely that the reported symptoms are caused by drug-related side effects from the medications. Although gastrointestinal symptoms were common in our evaluation, most previous studies report that DEC-induced gastrointestinal disturbance occurs when DEC is given at doses greater than >1 g orally; stomach upset develops less commonly when doses are <500 mg. We rarely saw the other less commonly reported side effects of DEC, namely nausea and fatigue. Albendazole is also unlikely to have caused the symptoms, because side effect rates are reported to be equivalent to those of placebo. It is possible that albendazole-mediated treatment of intestinal helminths may have caused gastrointestinal symptoms, because prevalence of these infections is fairly high. Baseline rates for specific intestinal helminths ranged from 11.2% to 34% in 2000 at four sentinel sites in Leogane, but infection prevalence and intensity were lower in 2004 after repeated rounds of MDA.

In addition to possible recall bias, these results are limited
by the small sample size and the fact that the study cohort may not be entirely representative of the population in Leogane Commune. Because the study sites were selected randomly from among the 20 with the most participants in prior years, there may have been a greater expectation of free symptomatic treatment at the selected sites. This might explain why study patients reported symptoms more frequently than the group of MDA participants overall. It is less likely that higher MF prevalence would explain the frequency of symptom reporting at the selected sites; these persons had a history of frequent MDA participation and were therefore less likely to be microfilaremic. It is possible (and likely) that these individuals may have been ICT positive before and that symptoms from previous MDAs resulted from filarial infection at that time. To assess statistical associations between MDA participation, ICT results, and symptom development, a control group would have been needed. Because of the logistics of running the survey from distribution points, it was not possible to recruit a control group. We also felt that for programmatic reasons, the most important group to target was that consisting of persons continuing to report symptoms.

The study of scrotal symptoms was also limited. Although the three examiners had extensive previous experience with scrotal examinations, it is possible that some nodules were missed on physical examination. Although nodules should have been detectable because they were tender to touch, they may not have become circumscribed by the time of examination.19 It is also possible that some of the ICT-negative men with scrotal pain and nodules on examination were actually infected with adult *W. bancrofti*. Limited data suggest that the antigen detection assays may be less sensitive in the setting of a low worm burden.27

The cost of treating post-MDA symptoms that are unrelated to the MDA or to LF infection poses a significant burden on the program; this money could perhaps be better used. Cost data from the 2002 MDA shows that $11,530 (7%) of the total MDA cost of $156,672 was spent on surveillance and treatment of adverse reactions.4 If adverse reaction funds were reallocated to the MDA itself, an additional 22,173 Haitians in Leogane could receive anti-filarial medication. It is possible that if Leogane’s LF program was to change its long-standing policy regarding free treatment of post-MDA symptoms, it could potentially decrease MDA coverage.11 That being said, study participants agreed to take part in future MDAs even if their potential symptoms were not treated (or treatment cost them money). A refusal rate of 18–22% among the symptomatic persons in Leogane (3.1% of all MDA participants) would remove a small percentage of the overall pool of MDA participants.

Other programs starting MDA might consider the effect that intensive surveillance and free treatment has on the reporting of minor symptoms. Issues for further consideration include the following: in areas of low MF prevalence, where adverse reactions are less likely, does one need active surveillance? In areas with higher MF prevalence (and a higher likelihood of adverse reactions after the first MDA), does one need to continue surveillance and treatment after the first year? Last, given the suggested target of treating the entire at-risk population for 4–6 years to end transmission, does offering free symptomatic treatment of post-MDA symptoms affect MDA coverage?28,29 The answers to these questions, which are faced by LF programs around the world, will likely vary country to country and program to program. Further studies of symptoms after MDA may shed additional light on the etiology of such symptoms and how to address them.

Received April 20, 2006. Accepted for publication July 10, 2006.

Acknowledgments: We thank the residents of Leogane Commune for participation; Denise Dor, Casseus Carlde, Elsie Boulin, Elaas Venus, and Carole Lafleur for work in administering the survey; John Williamson for reviewing the manuscript; and Dr. Thomas Streit for his valuable support for LF elimination in Haiti.

Financial support: Funding for this project was provided by the Emerging Infectious Disease Program at the Centers for Disease Control and Prevention.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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