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Burden of *Fasciola hepatica* Infection among Children from Paucartambo in Cusco, Peru

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Abstract. There is a high prevalence of fascioliasis in the Peruvian highlands, but most cases remain undiagnosed. The burden of disease caused by chronic subclinical infection is largely unknown. We studied school-age children from a district in Paucartambo Province in Cusco, Peru to evaluate the burden of disease caused by subclinical fascioliasis. Parasite eggs and/or larvae were identified in 46.2% of subjects, including *Fasciola hepatica* in 10.3% of subjects. Fascioliasis was independently associated with anemia (adjusted odds ratio = 3.01 [1.10–8.23]). Subclinical fascioliasis was common among children and strongly associated with anemia. Anemia should be recognized as an important component of the burden of disease from fascioliasis.

BACKGROUND

Fascioliasis has emerged as a significant public health problem among humans in developing countries and has been identified as one of the key neglected tropical diseases.[1,2] The infection prevalence in the Bolivian and Peruvian highlands are the highest in the world reaching 70%.[3] Nonetheless, the burden of disease caused by *Fasciola* is probably underestimated because of the poor sensitivity of diagnostic tests, limited available epidemiological data, and a poor understanding of the impact of subclinical illness. When symptomatic, fascioliasis has an acute phase caused by juvenile parasite migration through the liver, and a chronic phase caused by adult infection of the biliary tract.[4–7] However, most cases of fascioliasis are likely to remain undiagnosed and long-term complications in this group of patients are not known.

School-age children are disproportionately affected by fascioliasis in endemic areas.[8] Chronic inflammation and bleeding into the biliary tree could cause anemia.[6] Anemia and iron deficiency can cause devastating long-term developmental impairment in children.[9] Weight loss has also been described with fascioliasis, but the extent of this problem and association with malnutrition are unknown. Other poorly characterized long-term complications may include liver fibrosis and cirrhosis, which could add to the burden of disease.[10,11] Thus, fascioliasis has potential severe long-term consequences among children in developing countries even when subclinical. Research on the extent and importance of illnesses associated with the infection is needed. We performed a pilot study on the prevalence of fascioliasis among school-age children in the Paucartambo province in the Peruvian highlands, assessing the impact of fascioliasis and other co-infections on markers of morbidity, including measures of anemia and malnutrition.

METHODS

Design. A cross-sectional study was performed at a health fair on apparently healthy school-age children. Children from six communities participated in the health fairs. The communities (Piscohuata, Queunacancha, Chinchayhuasi, Huaqaycancha, Ohuay, and Huayllapata) are all in Huancarani district in Paucartambo province (northeast of Cusco city), Peru and at high elevation (~3,850 m). Data collected between November and December of 2010 included age, gender, place of residence (community), height, and weight. Automated hemoglobin and red cell indices were measured by cyanide-free colorimetric and impedance assays (Mindray BC3000 plus hematology analyzer, Shenzhen, China). Parasite eggs and larvae were detected in stools by direct and sedimentation tests performed on one stool specimen. The rapid sedimentation technique modified by Dr. Lumbreras, which is among the most sensitive concentration techniques to detect *F. hepatica* eggs, was used as described previously.[12,13]

Assessment for parasite infection. Children were considered infected if parasite eggs or larvae were identified by the direct and/or sedimentation stool exams. *Blastocystis hominis* was not considered a pathogen because children included in the study did not have diarrhea at the time of the intervention.

Assessment of anemia. Test results for hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were used to assess the presence and type of anemia. Hemoglobin values were adjusted for chronic high altitude exposure using formulas proposed by the Center for Disease Control and Prevention (CDC) and Dirren and others.[14,15] Age-specific cutoff values for hemoglobin and corpuscular constants proposed by the World Health Organization (WHO) were used to assess anemia and its characteristics.[16]

Assessment of nutritional status. Age, gender, height, and weight were used to assess the nutritional status of children. Stunting and malnutrition were defined according to the 2007 WHO growth standards and criteria for stunting and malnutrition.[17] The open access syntax file for SPSS software provided by WHO (http://www.who.int/growthref/tools/en/) was used to calculate the parameters z-scores. Stunting, a measure of chronic malnutrition, was assessed with the height for age z-score. Underweight, a measure of both acute and chronic malnutrition, was assessed with the weight for age z-score in children < 10 years of age and with the body mass index (BMI) z-score in children ≥ 10 years of age.[18] The z-scores were considered abnormally low when two standard deviations below the mean.

Statistical analysis. The SPSS version 18 software (SPSS, Inc., Chicago, IL) was used for the statistical analysis. The prevalence of fascioliasis, anemia, and nutritional deficiencies were calculated. Means (±SD) and medians with interquartile range (IQR) were used to compare age, anthropometric measurements, and hematologic test results. The *t* test was

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used to compare means between patients with fascioliasis and patient without fascioliasis. Odds ratios (ORs) with 95% confidence intervals were calculated to describe the variables associated with anemia, malnutrition, and *Fasciola* infection. Backward logistic regression analysis was used. Variables were included in the model using the likelihood ratio test. A $P < 0.05$ was considered statistically significant. The observed power analysis was performed for each test. Only charts with complete data were used for the multivariate analysis.

Ethical considerations. The study protocol was approved by the University of Texas Medical Branch Institutional Review Board. Subjects diagnosed with fascioliasis and other parasitic diseases were provided treatment at no cost.

RESULTS

A total of 255 charts from participating children were available. Only 223 (87.4%) charts had data on stool direct and sedimentation tests. Data on height, weight, and hematologic tests results were available in 232 (90.9%) charts. Records from 200 (78.4%) children had complete data and were used for the multivariate analysis. The mean age of the participants was 9.4 years (±2.1) and 126 of 255 (49.4%) were male. The place of residence was Huacaycancha for 57 of 255 (22.4%), Ohuay for 56 of 255 (22.0%), Piscohuata for 48 of 255 (18.8%), Huayllapata for 38 of 255 (14.9%), Chinchayhuasi for 29 of 255 (11.4%), and Queunacancha for 27 of 255 (10.6%) children. The mean height was 124.2 cm (±10.5) and the mean weight was 26.9 kg (±6.4). Children's characteristics stratified by place of residence are shown in Table 1.

Parasite eggs and/or larvae were identified in the stools of 103 of 223 subjects (46.2%). The overall prevalence of fascioliasis was 10.3% (23 of 223), ranging from 3.1% (1 of 32) in Piscohuata to 16.6% (6 of 36) in Huayllapata (Table 1). Male subjects were less likely to have fascioliasis than female subjects (6 of 107 versus 17 of 116, OR = 0.3 [0.1–0.9]). The mean age of children with fascioliasis was slightly older than those without the infection (118.3 months [±23.4] versus 113.4 months [±25.6]), but this difference was not statistically significant ($P = 0.3$, 1-β = 0.40). Children were also diagnosed with *Ascaris lumbricoides* (16.1%, 36 of 223), *Giardia* spp. (14.3%, 32 of 223), *Hymenolepis nana* (9.8%, 22 of 223), *Trichuris* spp. (1.3%, 3 of 223), and *Strongyloides stercoralis* larvae (1.3%, 3 of 223). In 24 of 223 (10.3%) of them more than one parasite was identified. No association was noted between having other intestinal parasites and age, gender, anemia, malnutrition, stunting, or fascioliasis.

The mean hemoglobin was 15.1 g/dL (±0.9) and was significantly lower in those with fascioliasis than those without *Fasciola* (14.6 g/dL versus 15.1 g/dL, $P = 0.01$, 1-β = 0.98). The mean hemoglobin using the CDC adjustment formula was 11.9 g/dL (±0.9 g/dL) and using the Dirren and others formula was 11.6 g/dL (±0.9 g/dL). The difference in mean hemoglobin between children with fascioliasis and children without fascioliasis remained significant after adjusting by the CDC (11.4 g/dL versus 11.9 g/dL, $P = 0.01$, 1-β = 0.98) and by the Dirren and others (11.1 g/dL versus 11.7 g/dL, $P = 0.01$, 1-β = 0.98) formulas. The age-adjusted prevalence of anemia was 37.3% and 51.8% using the CDC and Dirren and others formulas, respectively. All subjects had normal age adjusted red cell indices. The results of the backward logistic regression analysis of anemia by the CDC formula and the Dirren and others formula are shown in Table 2.

The median weight for the age z-score was –0.4 (IQR = –0.9–0.0) in children < 10 years of age. The prevalence of underweight in this group was 4.7% (6 of 127). The median BMI for age z-score was 0.1 (IQR = –0.3–0.5) among children 10 years of age or older. The prevalence of underweight among these children was 1.0% (1 of 105). No significant differences in gender, age, place of residence, prevalence of fascioliasis, or other parasites were found in underweight subjects compared with those without the condition. When comparing *Fasciola*-infected children with uninfected children no significant differences in the mean z-scores calculated for weight for age (–0.6 versus –0.5, $P = 0.6$, 1-β = 0.55) and BMI for age (0.2 versus 0.2, $P = 0.70$, 1-β = 0.80) were found. The median height for age z-score was –1.6 (IQR –2.3 to –1.0) and the prevalence of stunting was 35.7% (82 of 230). The mean age of stunted children was significantly higher than that of children with normal height (127.2 months (±24.2) versus 105.6 months (±23.5), $P < 0.01$, 1-β = 0.99). Similarly, there was a significant variation in the prevalence of stunting depending on the place of residence (Ouhay 62.7%, Huallapata 42.8%, Chinchayhuasi 26.6%, Queunacancha 26.9%, Piscohuata 25.5%, Huacaycancha 21.4%, $P < 0.01$). No significant association between stunting and gender, or infection with other parasites was found. Similarly, no significant differences in the mean z-score for height for age was found between children with fascioliasis and uninfected children (–1.5 versus –1.7, $P = 0.50$, 1-β = 0.33). In the backward logistic regression analysis only age was retained in the model (adjusted OR = 0.96 (0.95–0.97), likelihood ratio = 32.0, *df* 1, $P < 0.01$, Cox & Snell $R^2 = 0.14$, 1-β = 0.99).

DISCUSSION

One in 10 of children included in the study had subclinical fascioliasis and almost half were infected with other

TABLE 1
Characteristic of study participants by place of residence

		Piscohuata	Queunacancha	Ohuay	Huayllapata	Huacaycancha	Chichayhuasi	
		N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*P*
Gender	Male	26 (54.2)	15 (55.6)	25 (44.6)	14 (36.9)	28 (49.1)	18 (62.0)	0.34
	Female	22 (45.8)	12 (44.4)	31 (55.4)	24 (63.1)	29 (50.9)	11 (38.0)	
Mean age	Months (±SD)	113.1 (±28.6)	104.4 (±21.6)	111.3 (±24.5)	119.0 (±27.6)	114.1 (±25.3)	114.0 (±28.8)	0.39
Other parasites	Yes	15 (46.9)	4 (16.6)	25 (49.0)	18 (50.0)	19 (35.2)	4 (15.4)	0.03
	No	17 (53.1)	20 (83.4)	26 (51.0)	18 (50.0)	35 (64.8)	22 (84.6)	
Fascioliasis	Yes	1 (3.1)	2 (8.3)	3 (5.9)	6 (16.6)	8 (14.8)	3 (11.5)	0.32
	No	31 (96.9)	22 (91.7)	48 (94.1)	30 (83.4)	46 (85.2)	23 (88.4)	

TABLE 2
Adjusted odds ratios for the variables associated with anemia retained by the logistic regression model*

	CDC formula	Dirren and others formula
Variables in the model	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age (months)	1.01 (1.00–1.02)	1.1 (1.0–1.3)
Gender (female)	1.72 (0.94–3.14)	NIM
Fascioliasis	3.01 (1.10–8.23)	2.9 (1.0–8.7)
Model summary	Likelihood ratio 10.3, *df* 3, $P = 0.01$, Cox and Snell $R^2 = 0.05$, 1-β = 0.79	Likelihood ratio 7.7, *df* 2, $P = 0.02$, Cox and Snell $R^2 = 0.03$, 1-β = 0.72

*Variables entered step 1: age, gender, place of residence, other parasite infections, fascioliasis, malnutrition, and stunting.
OR = odds ratio; CI = confidence interval; NIM = not in the model.

gastrointestinal parasites. The prevalence of these parasites varied significantly within the same district. Normocytic normochromic anemia and stunting were common. Fascioliasis was significantly associated with anemia after adjusting for place of residence, age, gender, nutritional status, and other parasites. These results are important to understand the burden of disease caused by fascioliasis in children from Cusco and warrant further discussion.

Half of the children studied were infected with pathogenic helminths or protozoa. Although, the prevalence of parasitic infections in other regions of Peru can be as high as 100%, the prevalence found in our study is significantly higher compared with studies at similar altitudes.[19] Maco and others[20] reported a prevalence of 2% and 6% for *A. lumbricoides* and *H. nana*, respectively, among the general population in the nearby Puno region at 3,800 m. Similarly, Cabrera and others[21] noted a lower prevalence of *A. lumbricoides* (4%) and *H. nana* (3%) in Ayacucho at above 3000 m. Socioeconomic factors are likely to play a role in the high prevalence of intestinal parasites found. The Paucartambo province is among the poorest regions in Peru with over 73% of people living with fewer than two dollars per day[22]; these conditions seem to play an important role in fecal-oral transmission of parasites. Poverty clearly influences access to clean water, safe food supplies, and proper excretal disposal, increasing the risk of transmission of intestinal parasites.[23,24]

More than 10% of children were diagnosed with fascioliasis in our study. This rate is similar to the prevalence reported in other parts of the Peruvian highlands that ranges from 6% to 68%.[25] There was significant variability in the prevalence of fascioliasis within communities in a small geographic region. This variability in prevalence within regions is characteristic of the epidemiology of fascioliasis as has been demonstrated in several other studies in Peru and Bolivia.[26,27] The reasons for these differences in prevalence are not well understood and multiple factors are likely to play a role. The distribution of the snail intermediary host and definitive host (mainly cattle and sheep) is important.[28] Human practices regarding sources of drinking water and consumption aquatic vegetation also play a role.[29] Of importance, the availability of water capable of supporting the lymnaeid snail hosts year round seemed crucial to maintain transmission.[30]

Only a minority of children was underweight, but almost one in three suffered from stunting, which is associated with poorer development in children.[31] Although, significant weight loss has been described as part of fascioliasis presentation in Lima, Peru; no association was found between fascioliasis and malnutrition in our study.[5] This contrasts with studies reported by Gyorkos and others[32] who noted that Peruvian children 7–14 months of age with moderate to heavy helminth infections were at increased risk for stunting. Likewise, Casapia and others[33] evaluated factors associated with stunting and underweight among fifth graders in the Peruvian Amazon. Heavy hookworm infection or *Ascaris* and *Trichuris* co-infection were associated with adverse nutritional outcomes.[33] Interestingly, no hookworm infections were identified in our study. Therefore, more detailed studies about helminth infections at high altitude are needed to gauge their impact on nutritional status.

Chronic helminth infections are subclinical and may remain undiagnosed. However, even when subclinical, these infections cause chronic inflammation and immune activation. These processes are associated with anemia, malnutrition, impaired development, and decreased productivity.[34] Children with fascioliasis included in our study did not complain of overt symptoms, despite a high prevalence of anemia and stunting. Anemia was significantly more common among children with fascioliasis compared with uninfected children even after adjusting for nutritional status and other helminth infections. Small studies in Peru have reported the presence of anemia in children with fascioliasis, but these lacked comparison groups to show the association between the infection and anemia.[6,8] El-Shazly and others noted that normocytic normochromic anemia was the most common type of anemia among Egyptian children infected with *Fasciola*. Of note, almost half of these children had a positive test for occult blood in stools.[35] Multiple factors are likely to play a role in the mechanisms of anemia in fascioliasis. Normocytic normochromic anemia is associated with chronic inflammation. Loss of blood in the gastrointestinal track may be associated with iron deficiency. This is especially important because of the long-term consequences of iron deficiency on cognitive function.[9] In addition, the effectiveness of current iron supplementation practices among children might be affected by *Fasciola* infection.

It is important to acknowledge the limitations of analyzing information retrospectively, in which the standardization of observations may have not been optimal. Two different hemoglobin adjustment formulas were used to approach the lack of validated hemoglobin adjustment formulas for children at 3,800 m. In addition to the comparison of age and altitude adjusted anemia prevalence between groups, the mean hemoglobin values were compared between groups to reduce the influence of the adjustment formula on the observed associations. Finally, microscopy testing on one stool specimen is an insensitive method to diagnose helminthic infections. Therefore, the prevalence of fascioliasis and other intestinal parasites was almost certainly underestimated in our study.

Because unrecognized cases were likely included with controls, our estimates of the effects of fascioliasis may have underestimated the effects on disease burden.

In conclusion, we have demonstrated that *Fasciola* infection is common among children in Paucartambo, Cusco, Peru. Malnutrition, anemia, and intestinal parasite infections were also common. Our results suggest that part of the burden of fascioliasis in hyperendemic areas is associated with subclinical manifestations like anemia. Further studies to define the burden of disease associated with fascioliasis and its public health importance are needed. An integrated approach to control diseases associated with poverty may need to account for *Fasciola* infection, which is resistant to medications typically used for deworming campaigns. Larger, prospective studies are urgently needed to clarify the association of *Fasciola* with conditions such as anemia and malnutrition, to determine the mechanisms involved in their pathogenesis, and to determine the most cost-effective interventions.

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