Parasitic helminth infection and cognitive function in school children

C. NOKES¹, S. M. GRANTHAM-McGREGOR², A. W. SAWYER¹, E. S. COOPER¹ and D. A. P. BUNDY¹

¹ Wellcome Trust Research Centre for Parasitic Infections, Department of Biology, West Wing, Imperial College, Prince Consort Road, London SW7 2BB, U.K.
² Tropical Metabolism Research Unit, Mona Campus, University of the West Indies, Kingston, Jamaica

SUMMARY

The study examines the effect of moderate to high worm burdens of *Trichuris trichiura* infection on the cognitive functions of 159 school children (age 9–12 years) in Jamaica, using a double-blind placebo-controlled protocol. Results were evaluated by using a forward-stepwise multiple linear regression. Removal of worms led to a significant improvement in tests of auditory short-term memory (*p* < 0.017; *p* < 0.017; *p* < 0.017; *p* < 0.017), and scanning and retrieval of long-term memory (*p* < 0.001). Nine weeks after treatment, there were no longer significant differences between the treated children and an uninfected Control group in these three tests of cognitive function. It is concluded that whipworm infection has an adverse effect on certain cognitive functions which is reversible by therapy.

The parasitic nematodes *Ascaris lumbricoides* and *Trichuris trichiura* are estimated to infect one quarter of the world’s population (World Health Organization, 1987). School-age children harbour both the highest prevalences and intensities of these geohelminth infections (Cooper & Bundy 1987), and the resulting morbidity involves undernutrition and iron-deficiency anaemia (Gilman et al. 1983; Stephenson 1987), both of which are associated with impaired cognitive function and learning ability (Grantham-McGregor 1990; Soewondo et al. 1989). An association between helminth infection and educational achievement has long been recognized (Stiles 1915; Strong 1916; Waite & Neilson 1919; Nokes et al. 1991; Pollitt 1990), however, it is unclear whether the relation is causal or results from covariance with socio-economic status (Halloran et al. 1989). This paper reports the results of a double-blind clinical trial to examine whether infection with the human whipworm, *Trichuris trichiura*, in children, is causally related to their cognitive function. The study design and held methodology are summarized in figure 1. A more detailed description of the protocol and experimental procedures is given elsewhere (Nokes et al. 1992).

Stool samples were requested from all children aged 9–12 years from three schools in Mandeville, Jamaica, and were screened for the presence and intensity of geohelminth eggs by using the Kato Thick Smear technique (Martin & Beaver 1968). Of the original 593 children, a second stool sample was examined, three months later, from 216 children to confirm their infection status. Of these, 104 children who had, on both occasions, a moderate to heavy worm burden of *T. trichiura* infection (more than 1900 parasite eggs per gram (epg) of faeces) and a zero or very low intensity of infection with the hookworm *Necator americanus*, were randomly assigned to treatment or placebo. Given the sample size, it was not possible to stratify the presence or intensity of *Ascaris lumbricoides* infection and therefore this was controlled for statistically at the end. Of the 80 children uninfected on both occasions, 56 were randomly assigned to a Control group for comparative purposes.

The cognitive function of children in all three groups was assessed by using a battery of eight tests which were administered both before and 63 ± 8 days after intervention, the time interval between cognitive tests corresponding to one school term. Intra-observer reliabilities were done before the commencement of the study with a correlation coefficient of *r*² > 0.70 set as the minimum acceptable level of test repeatability for inclusion in the clinical trial. The tests had previously been done by Jamaican children of a similar age, and were culturally acceptable (Simeon & Grantham-McGregor 1989). These tests were chosen because in factor analysis they load on a ‘freedom from distractibility’ factor (Kaufman 1975). One person (C.N.) administered all the cognitive tests. Three tests, Digit-Span Forwards/Backwards, Arithmetic and Coding, were taken from the Wechsler Intelligence Scale for Children (WISC) because they involve attention and distractibility, and it has been suggested that these functions are most likely to be affected (Pollitt 1990). Short-term memory also contributes to each of these three tests, as well as computational and clerical skills in Arithmetic and Coding, respectively. Other tests included: the Matching Familiar Figures test (MFFT), which involves problem solving abilities; Listening Comprehension, involving memory and information processing, and which also resembles work done in...
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Figure 1. Schematic diagram of experimental design and fieldwork methods. Time interval between cognitive tests = 63 ± 8 days per individual.

Each child assigned to the Treatment group, received three daily 400 mg doses of the broad spectrum anthelminthic, albendazole (Zentel; SmithKline Beecham Pharmaceuticals) following initial cognitive testing. The Control and Placebo groups both received a matching placebo.

A minimum of ten days after treatment, a stool sample was examined from each child to confirm the infection status of the Control and Placebo children and to determine the effectiveness of helminthic expulsion in the Treatment group. Treatment resulted in a reduction of faecal egg density (epg) of more than 95% in 98% of children with *T. trichiura* and a reduction in eggs of more than 99% in 98% of children with *A. lumbricoides* and *N. americanus*. These reductions indicate a highly significant (*p < 0.0001*) reduction in worm burden. Complete cure was achieved for 79% and 97% of *T. trichiura* and *A. lumbricoides* infections,

Table 1. Baseline characteristics of infected and uninfected groups

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>placebo</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>infection status (epg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>T. trichiura</em></td>
<td>5 (30.3)*</td>
<td>8239 (4857.9)</td>
<td>10897 (19818.0)</td>
</tr>
<tr>
<td><em>A. lumbricoides</em></td>
<td>139 (934.7)*</td>
<td>24298 (43889.7)</td>
<td>36012 (65120.4)</td>
</tr>
<tr>
<td><em>N. americanus</em></td>
<td>0 (0.0)*</td>
<td>46 (149.4)</td>
<td>64 (199.4)</td>
</tr>
<tr>
<td>age/years</td>
<td>10.1 (0.7)*</td>
<td>10.4 (0.7)</td>
<td>10.6 (0.7)</td>
</tr>
<tr>
<td>height for age (%)</td>
<td>99.8 (4.7)*</td>
<td>99.4 (4.9)</td>
<td>96.3 (4.5)</td>
</tr>
<tr>
<td>mass for height (%)</td>
<td>95.3 (11.4)*</td>
<td>94.6 (8.0)</td>
<td>94.2 (7.9)</td>
</tr>
<tr>
<td>haemoglobin / g/dl</td>
<td>12.8 (1.1)</td>
<td>12.4 (1.7)</td>
<td>12.8 (1.1)</td>
</tr>
<tr>
<td>FEP/pg per gHb</td>
<td>2.3 (1.5)</td>
<td>2.4 (1.6)</td>
<td>2.2 (1.1)</td>
</tr>
<tr>
<td>socio-economic status (ses)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>housing-utilities (0-10)</td>
<td>6.3 (3.6)*</td>
<td>3.9 (3.3)</td>
<td>3.2 (3.0)</td>
</tr>
<tr>
<td>uniform rating (1-15)</td>
<td>8.9 (2.5)*</td>
<td>7.1 (2.8)</td>
<td>7.4 (2.4)</td>
</tr>
<tr>
<td>crowding (1-4)</td>
<td>1.1 (0.8)*</td>
<td>1.3 (0.8)</td>
<td>1.4 (0.8)</td>
</tr>
<tr>
<td>educational opportunity (5-120)</td>
<td>34.9 (22.4)*</td>
<td>23.5 (16.9)</td>
<td>22.9 (15.8)</td>
</tr>
<tr>
<td>iq (Ravens matrices)</td>
<td>21.0 (6.9)*</td>
<td>15.7 (5.7)</td>
<td>15.9 (5.4)</td>
</tr>
<tr>
<td>absenteeism (proportion of year)</td>
<td>0.12 (0.1)</td>
<td>0.28 (0.1)</td>
<td>0.27 (0.1)</td>
</tr>
</tbody>
</table>

* T-test, *p < 0.0001.
* T-test, *p < 0.01.
* Mann-Whitney U test, *p < 0.0005.
* Mann-Whitney U test, *p < 0.05.

**Note:** For Table 1, significant differences between the uninfected Control and the combined infected groups (Treatment and Placebo) are shown. Socio-economic status (ses) was determined by questionnaire (modified from Clarke et al. 1991). Scores are defined as follows: Housing–utilities score: the availability of water and toilet utilities and the number and type of household items. Uniform rating: the number and condition of clothes worn to school. Educational opportunity: the number of exercise and text books bought by the parent and currently being used plus the receipt of paid lessons after school hours. Principal component analysis was used to weight the individual components of these variables to formulate composite scores (Jolliffe 1986). Height and mass are expressed as a percentage of the NCHS standards (NCHS growth charts 1976). Mean ± (s.d.).
respectively. There was no significant change in the prevalence and intensity of geohelminth infection in the Control and Placebo groups.

The initial intensities of the three parasites were not significantly different between the Treatment and Placebo groups. The baseline characteristics, initial cognitive scores and IQs of the infected Treatment and Placebo groups were also similar, differing, because of chance, only in height for age (ANOVA; Scheffe's; \(p < 0.01\)) (tables 1 and 2). The uninfected Control group showed that, in three cognitive tests, heights for age and school attendance than the combined infected groups, and they also had a significantly better performance in all the cognitive tests and IQ (tables 1 and 2).

Forward-stepwise multiple linear regression was used to analyse how the tests of cognitive function in the Treatment and Placebo groups changed over time. In each regression the dependent variable was the final cognitive score, and the independent variables offered into the multiple regression equation were: initial cognitive score, the child's group entered as a categorical variable defining group status was Treatment/Control (coded as 1/0). The intensity of infection was important in determining a response, the intensities of A. lumbricoides and T. trichiura infection were offered into those regressions comparing the Treatment and Placebo groups. The importance of the presence or absence of A. lumbricoides was analysed by the inclusion of the interaction term A. lumbricoides (presence/absence) \(\times\) intervention group (Treatment/Placebo) into each linear regression model. To avoid collinearility with the independent variables were checked for normality and linearity with the dependent variable before doing the regression analysis. Independent variables were removed from the regression if they were highly correlated with a variable already present in the model. The unique contribution of each variable could therefore be assessed. Normality of the residuals was confirmed by using the Kolmogorov-Smirnov test. The final model was checked to ensure no assumptions had been violated (Bowerman & O'Connell 1990). All statistical procedures were done using the SAS for Unix package.

Multiple linear regression was also used to compare the Treatment and Control groups. The model was similar to the one used above, except this time the categorical variable defining group status was Treatment/Control (coded as 1/0). The intensity of geohelminth infection was not offered because the Control group was uninfected. By controlling for the important confounding variables first, the improvement in the Treatment group over and above the Control group could be measured despite differences in their baseline characteristics.

The rates of improvement in the Placebo and Control groups were compared by using Mann-Whitney U test on the differences in slope. This simple procedure was considered adequate in explaining whether both groups improved at similar rates despite their initial differences.

During the study, one child in the Placebo group was lost to follow-up, and a small number, which varied for each test (four to ten), were excluded from analysis because of inadequate test conditions, such as a test being interrupted.

Multiple regression analysis of the Treatment and Placebo groups showed that, in three cognitive tests, children who received anthelminthic treatment improved significantly more than those who received placebo (table 3). This was indicated by the positive and significant regression coefficient of the categorical
variable Treatment (1)/Placebo (0). This significant treatment effect was observed in the tests of Fluency ($p < 0.001$), Digit-Span Forwards ($p < 0.02$) and Digit-Span Backwards ($p < 0.01$). In no other test was the effect of treatment significant.

As a proportion (61%) of the infected children also had *A. lumbricoides*, the interaction term was included to determine whether it was the removal of *T. trichiura* or *A. lumbricoides* or both infections which led to the observed improvement. In no regression was the presence of *A. lumbricoides* a significant factor ($p > 0.1$). The importance of the initial intensity of infection with *T. trichiura* and *A. lumbricoides* was also analysed within the same model, but in no regression was the intensity of either parasite selected as being significant.

When the multiple regressions were repeated on the Treatment and Control children, the treatment group was shown to have improved significantly more than the Control group in Fluency ($p < 0.003$) and Digit-Span Forwards ($p < 0.05$) and Digit-Span Backwards ($p < 0.01$). Again, this was indicated by the positive regression coefficient of the categorical variable (Treatment (0) Control (1)) which, even after controlling for important confounding variables, contributed significantly to the observed differences in cognitive function. On completion of the study, there were no longer any significant differences (ANOVA; Scheffé's, $p > 0.1$) in the performance scores for these three cognitive tests.

The Control and Placebo group had significantly different scores in each test of cognitive function both pre- and post-intervention (ANOVA; Scheffé's, $p < 0.05$) in all tests except for Arithmetic (post-intervention) and the hard items of the MFFT (pre-intervention). There was no significant difference in the rate of improvement in cognitive function between the two groups despite differences in their social background characteristics.

The study did not aim to investigate the mechanism by which worms may affect cognitive function, but undernutrition with or without anaemia was considered to be of potential importance. Both conditions are commonly reported in *T. trichiura* infection (Bundy 1986; Cooper *et al.* 1990), and are also known to affect cognition and learning ability (Grantham-McGregor 1990; Soewondo *et al.* 1990; reviewed in Pollitt 1990). However, in this study, baseline anthropometry and iron status did not significantly contribute to the observed differences in cognitive test performance. This may be caused by the absence of any initial deficit in iron status and mass-for-height in the infected groups, coupled with the short time interval between cognitive testings, which was perhaps insufficient to permit a measurable change to occur.

A possible explanation of the way in which helminths affect cognition is through their effects on the general well-being of the infected child. The fatigue and listlessness experienced by children suffering from moderate to heavy loads of *T. trichiura* (Cooper & Bundy 1987) may result in a suboptimal level of arousal (Eysenck 1976) with children being less able to perform well in the tests. Knowledge of the mechanism by which worms affect cognition is clearly an important area of research which needs to be explored.

This is the first study to demonstrate that moderate to heavy loads of *T. trichiura* have a detrimental and reversible effect on certain cognitive functions in children. Considering the high global prevalence of infection, further studies are urgently required to determine whether the effect of infection has longer term implications for school achievement.

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