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Original Article

The effect of treatment for soil-transmitted helminthiasis on cognitive function in children

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Abstract

Background Soil-transmitted helminth (STH) infections affect one-third of the world's population. School-aged children are reported to have the highest prevalence and intensity of disease, resulting in impaired cognitive function, malnutrition and morbidity.

Objective To examine differences in cognitive function in STH-infected children before and after treatment.

Methods We conducted a randomized, open-label, controlled trial from November 2008 - March 2009 in Aek Nabara, Labuhan Batu District, North Sumatera Province. Subjects were primary school-aged children with STH infection. Before intervention, data on age, sex, nutritional status, STH infection status and cognitive function were collected. Subjects were divided into two groups by simple randomization. Group I received 400 mg albendazole and group II received a placebo. Three months after intervention, cognitive function of subjects in both groups was reassessed. Data was analysed by Student's t test, with P value of less than 0.05 considered to be statistically significant.

Results Cognitive tests with the Wechsler Intelligence Scale for Children (WISC) were performed in 120 children infected with STH. Sixty children received 400 mg albendazole and 60 children received placebo. Seven children were excluded and one dropped out from this study. Three months after the intervention, we reevaluated cognitive function and found significant differences in the categories of digit span (P=0.024) and total IQ score (P=0.027) between the two groups.

Conclusions Treatment of STH infection with albendazole improved cognitive function of children in comprehension, coding and digit span testing. Performance and full IQ scores were also improved after treatment. **[Paediatr Indones. 2012;52:99-105]**.

Keywords: *soil-transmitted helminth, cognitive, children*

Approximately one-third of the world's population is infected with one or more helminth species, parasites which reside in the gastrointestinal tract.[1-3] School-aged children in developing countries suffer the most from this condition.[4-6] Several studies have shown a relationship between helminthiasis and poor nutrition, iron deficiency anemia, growth retardation and poor intelligence.[7,8]

About twenty species of helminths are able to infect humans, but the most common of these is the soil-transmitted helminth (STH). One-third of world human population is infected with one or more of the following helminthes: *Ascaris lumbricoides*, *Necator americanus*, *Ancylostoma duodenale* and *Trichuris trichiura*.[9] These helminths share similar epidemiological characteristics.[10,11]

Children and young adults have the highest prevalence and intensity of helminth infections. Roundworm and whipworm cause the most severe infections in children aged 5 – 10 years, while hookworm causes the most severe infections in

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children over 10 years of age.[10,11] Soil-transmited helminths can cause symptoms such as diarrhea, abdominal pain, poor weight gain, malnutrition, anemia, and poor intelligence.[12,13]

The effects of STH infections have been widely studied and reported to cause low intelligence. A study in the Philippines showed that moderate and high intensity of ascariasis was related to poor memory, while trichuriasis was related to low verbal intelligence. Abdominal pain during ascariasis and trichuriasis distracts a child's attention and causes poor concentration in performing intelligence tests.[5] An Indonesian study showed that hookworm infection caused poor memory, resulting in impaired analyzing ability.[6]

The aim of our study was to examine differences in cognitive function before and after treatment of STH infection in children.

Methods

We conducted an open-label, randomized, controlled trial to examine differences in cognitive function before and after treatment of STH infection in children.

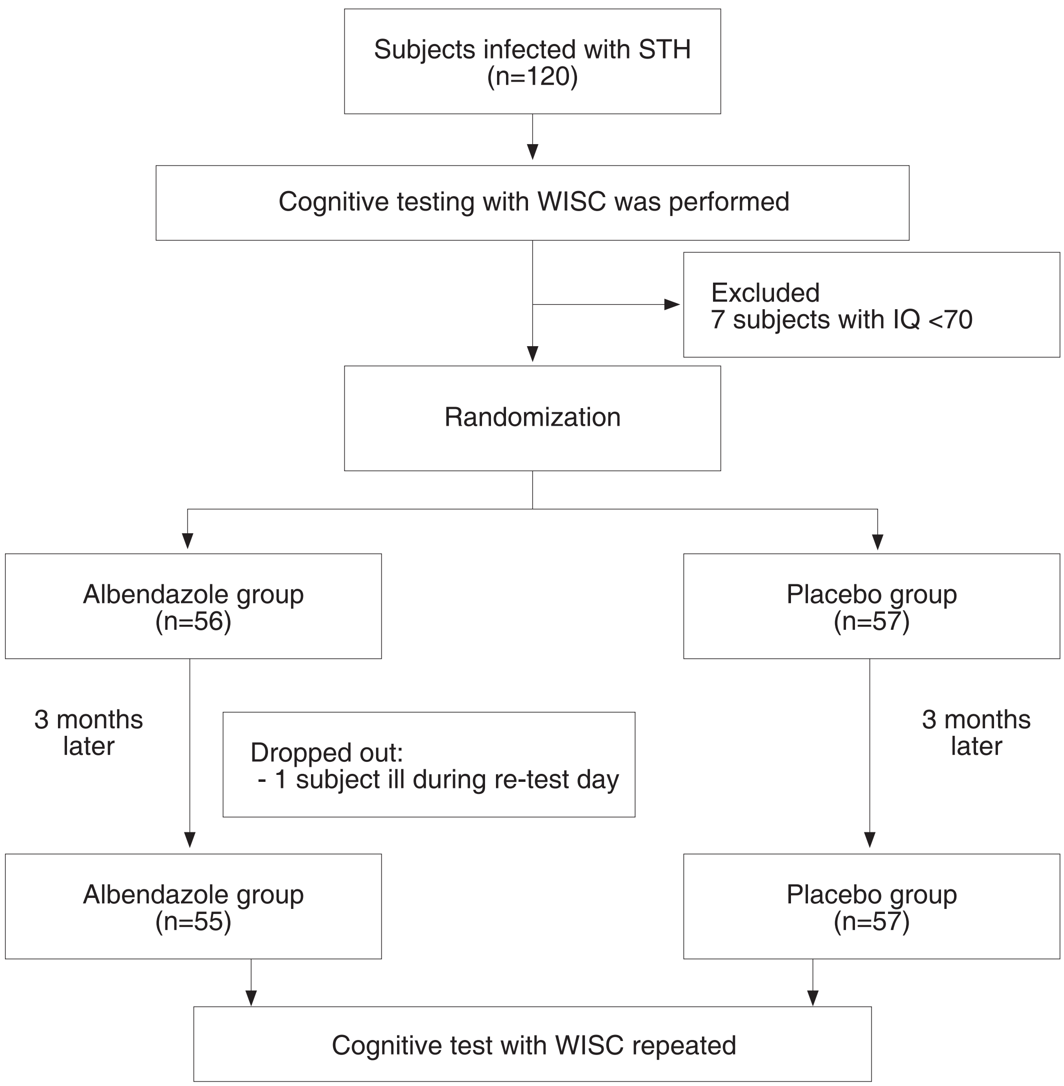

Figure 1. Study profile

Our study was conducted from November 2008 - March 2009 in Aek Nabara, Labuhan Batu District, North Sumatera Province. Study subjects were primary school-aged children infected with STH. The required sample size was calculated to be 53 subjects per group. We included primary school-aged children infected with STH, who had no recent prior treatment for helminthiasis, and agreed to participate in the study. We excluded children who refused to take the medication or perform the cognitive test, did not cooperate in stool sample collection, suffered from other diseases (e.g., epilepsy), had an intelligent quotient (IQ) lower than 70, or were allergic to albendazole.

Before starting the study, we explained the study methods, as well as the effects of STH infection and antihelmentic treatment to subjects and their parents. Before the intervention, data on age, sex, nutritional status, STH infection status and cognitive function were collected. All subjects' stool specimens were examined by the Kato Katz method to count soil-transmitted eggs. Subjects were randomized into two groups, the albendazole (400 mg single dose) group and the placebo group. Cognitive testing was performed by a psychologist before and three months after the intervention. Cognitive function was assessed by WISC.

We analyzed the data by SPSS version 14.0. The association between STH infection and cognitive function was analysed by Student's t test. The significance level was accepted as $P < 0.05$, with a 95% confidence interval (95% CI).

Results

One hundred twenty subjects with STH infections were enrolled, 7 subjects were excluded because of low IQ score (< 70). The rest were randomly assigned to receive a single dose of 400 mg albendazole (n = 56) or placebo (n = 57). In addition, one subject in albendazole group was dropped out due to illness on testing day, leaving a total of 112 subjects who completed the study. The study profile is shown in **Figure 1**.

Baseline characteristics were similar between the two groups, as shown in **Table 1**.

In both groups, most subjects had mild STH infections, based on stool egg counts of *Ascaris lumbricoides* and *Trichuris trichura*. In the albendazole group, we found mild ascariasis in 49 subjects (89.1%) and mild trichuriasis in 48 subjects (87.3%), while in the placebo group, we found mild ascariasis in 44 subjects (77.2%) and mild trichuriasis in 51 subjects (89.5%).

Three months after treatment, subjects in the albendazole group showed better cognitive function than subjects in the placebo group, in the categories of digit span (P=0.024) and total IQ score (P=0.027).

Table 1. Baseline characteristics of subjects

Characteristics	Group I (albendazole) n=55	Group II (placebo) n=57
Gender, n (%)		
- Female	27 (49.1)	30 (52.6)
- Male	28 (50.9)	27 (47.4)
Mean age, years (SD)	9.6 (1.75)	9.6 (1.72)
Mean weight, kg (SD)	23.9 (6.63)	24.7 (4.13)
Mean height, cm (SD)	121.7 (8.87)	124.8 (5.53)
Nutritional status, n (%)		
- Severe malnourished	3 (5.5)	1 (1.8)
- Moderate malnourished	3 (5.5)	3 (5.3)
- Mild malnourished	9 (16.4)	11 (19.3)
- Well nourished	31 (56.4)	35 (61.4)
- Overweight	4 (7.3)	6 (10.5)
- Obese	5 (9.1)	1 (1.8)
STH egg intensity, n (%)		
Ascaris lubricoides		
- Negative	6 (10.9)	8 (14.0)
- Mild	49 (89.1)	44 (77.2)
- Moderate	0	5 (8.8)
- Severe	0	0
Trichuris trichiura		
- Negative	7 (12.7)	6 (10.5)
- Mild	48(87.3)	51 (89.5)
- Moderate	0	0
- Severe	0	0
WISC test results		
Mean verbal scores (SD)		
- Information	9.6 (2.88)	8.8 (3.02)
- Comprehension	6.4 (3.39)	6.8 (2.90)
- Arithmetic	8.9 (2.71)	8.6 (2.34)
- Similarities	9.3 (3.43)	9.8 (2.97)
- Digit span	7.8 (2.88)	7.6 (2.87)
- Total verbal score	41.1 (10.96)	41.3 (9.38)
- Verbal IQ	88.8 (13.75)	89.1 (11.65)
Mean performance scores (SD)		
- Picture completion	7.6 (2.54)	7.3 (2.88)
- Picture arrangement	7.3 (2.57)	7.2 (1.99)
- Block design	9.4 (2.69)	8.7 (2.71)
- Object assembling	7.2 (3.30)	6.8 (3.39)
- Coding	11.3 (3.28)	11.3 (3.78)
- Total performance score	42.8 (9.03)	41.4 (9.13)
- Performance IQ	88.3 (13.75)	87.8 (12.17)
Mean total IQ (SD)	88.5 (12.02)	88.9 (12.88)

Table 2. Comparison of cognitive test results between the albendazole and placebo groups three months after intervention

Variable	Albendazole		Placebo		P
	Mean	SD	Mean	SD	
Verbal					
Information	9.5	2.69	9.3	2.93	0.742
Comprehension	7.5	2.69	6.9	2.89	0.321
Arithmetic	9.3	2.74	8.7	2.37	0.256
Similarities	9.7	3.12	9.5	2.89	0.681
Digit span	8.1	2.47	7.0	2.41	0.024
Total verbal score	44.0	8.64	41.1	8.83	0.084
Verbal IQ	90.6	16.10	88.7	11.16	0.481
Performance					
Picture completion	8.3	3.10	7.4	2.79	0.088
Picture arrangement	8.0	2.13	7.7	2.18	0.465
Block design	9.4	2.83	9.1	2.63	0.307
Object assembling	7.5	3.17	7.1	3.93	0.568
Coding	12.6	3.88	11.3	3.67	0.063
Total performance score	46.2	9.68	42.9	9.36	0.074
Performance IQ	94.3	13.03	89.8	12.49	0.068
Total IQ	93.4	12.32	88.5	11.02	0.027

Other subtest scores were not significantly different between groups. **Table 2** shows the comparison of cognitive test results between the albendazole and placebo groups three months after intervention.

Discussion

We revealed that the prevalence of STH infection in Aek Nabara, Labuhan Batu District, North Sumatera Province was 33.8%. Our study included 112 subjects with mild to moderate ascariasis and/or trichuriasis. Soil-transmitted helminth infection has been reported to be highly prevalent, 60% to 90% for *Ascaris lumbricoides*, 40% to 60% for *Trichuris trichiura* and 10% for hookworm.[1,2] These infections cause several morbidities including malnutrition, iron deficiency anemia and poor intelligence.[3,4] Studies on the relationship between STH infections and cognitive function have focused on school-aged children since they are more susceptible to STH infection and tend to have greater cognitive consequences of infection.[6,7]

Our results were similar to those of previous studies on the relationship between STH infection and cognitive function. The WISC showed better cognitive results in the albendazole group than in the placebo group. The mechanism of improved cognitive function was not analysed. This improved cognitive function could be a direct cause of STH eradication and diminished STH clinical manifestations or indirect mechanisms. Poor cognitive function during STH infection is caused by many factors, direct and indirect. Helminth movement inside the gastrointestinal tract may distract the concentration of an infected child. Helminth-infected children suffer stomach aches, sleep disorders and malaise, all of which may lead to poor school performance. Treatment of the STH infection will improve a child's appetite, diminish stomachaches and headaches.[10] A limitation of our study was that we did not examine symptoms caused by STH and their effects on subjects' cognitive function, so we could not determine whether the impaired cognitive function was a direct or indirect caused of STH infection.

Soil-transmitted helminths indirectly affect cognitive function by stimulating an immune response and disturbing nutritional intake. Helminths compete for nutrition in the gastrointestinal tract by directly consuming nutrients and blood, causing malabsorption, secretion of protease inhibitors and stimulation of an immune response, leading to eventual anorexia. Malnourished children have poor concentration. The main reason for poor cognition during STH infection was reported to be low iron level.[10,14] Iron deficiency anemia will cause a low iron level in the brain, leading to hypomyelinization and dopaminergic disorders.

These patients are more susceptible to stress, leading to behavior disorders and learning difficulties.[15] Children with hemoglobin levels lower than 10.5 g/dl for more than three months show poor development test results, mainly in language skills.[16] In our study, we found malnourishment in 27.4% of subjects in the albendazole group and 26.3% of subjects in the placebo group. We observed well-nourished subjects in 56.4% and 61.4% of subjects in the albendazole and placebo groups, respectively. We did not examine whether the malnutrition was caused by helminthiasis or poor nutrient intake.

Several studies have shown that antihelmentic therapy, as well as iron[17-19] and micronutrient supplementation,[20] leads to higher hemoglobin levels and better micronutrient status, both of which improve cognitive function.[21] A study from Zaire reported that rural African children with better nutrition had better cognitive development in response to economic and educational program development.[22] A meta-analysis supported the previous study's results, concluding that treatment for nematodes and food supplementation increased body weight and growth.[23] Worsened anemia occurred during heavy intensity hookworm infection,[24] and children with growth retardation had poorer cognitive test results than children without growth retardation.[25] Decreased brain weight, increased liquid composition in brain and reduced myelin during malnutrition correlate to the length of the starvation period. Significant effects on the brain occur if the insult happens during a rapid growth period of neurons or synaptogenesis.[26] We found some mildly to severely malnourished children in our study, but the relationship between malnutrition and cognitive function was not analysed. We gave only antihelmentic therapy, without food or iron supplementation, and observed improved cognitive function.

Helminthiasis has been shown to be correlated with the release of several cytokines, though not previously well-specified. A common immune-mediated behavior disorder in helminthiasis is anorexia, which is suspected to be caused by the release of mediators, such as interleukin-1, tumor necrosis factor-α and interleukin-6. Anorexia decreases nutrient intake, leading to poor nutritional status and lower cognitive function.[10] Cytokine release may cause behavior disorders, poor memory and loss of concentration.[27] The relationship between cytokine release in STH infection and cognitive function was also not examined in our study.

The relationship between helminthiasis and cognitive function has been widely studied.[28] An open-label, randomized, controlled trial conducted in Jamaica in six to twelve year-old children examined their growth, cognitive function and school attendance before and after albendazole intervention. The study showed that trichuriasis treatment improved school performance in children with poor nutrition and increased body weight in mildly infected children.[29] Another randomized, controlled trial in Indonesia showed that treatment of ascariasis with mebendazole improved learning ability, concentration, and coordination.[30]

A prospective cohort of 7 - 18 year-old children in the Philippines showed that *Schistosoma japonicum* infection correlated with poor learning ability; *Ascaris lumbricoides* infection correlated with poor memory, and *Trichuris trichiura* infection correlated with poor verbal fluency.[5] Sakti *et al.* showed that hookworm infection negatively affected memory and caused lower scores in fluency, digit span forward, number choice, picture search, Stroop color-word test, and maze test.[6] A cross-sectional study in Tanzania showed that heavy intensity helminthiasis with poor nutrition caused poor intelligence in working memory.[7] A double-blind trial in Jamaica showed that helminthiasis affected children's cognitive function in the digit span subtest.[31]

WHO recommends four essential antihelmintics: albendazole, mebendazole, levamisole, and pyrantel pamoate, to effectively control morbidity in endemic areas, if given regularly.[32] We used albendazole based on the WHO recommendation, and looked for any relationship between STH infection and cognitive function. Several factors that can affect cognitive function, other than STH infection, were not analyzed in this study. Other study limitations were our small sample size and not assessing the effects of socio-economic status, parental education, environmental hygiene and hemoglobin levels on subjects' cognitive function.

In conclusion, the comparison of cognitive test results of the albendazole and placebo groups showed that the albendazole group had better digit span and total IQ score than the placebo group, three months after albendazole treatment.

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