EARLY CHILDHOOD DIARRHEA IS ASSOCIATED WITH DIMINISHED COGNITIVE FUNCTION 4 TO 7 YEARS LATER IN CHILDREN IN A NORTHEAST BRAZILIAN SHANTYTOWN

MARK D. NIEHAUS, SEAN R. MOORE, PETER D. PATRICK, LORI L. DERR, BREYETTE LORNTZ, ALDO A. LIMA, AND RICHARD L. GUERRANT

Brown University, Providence, Rhode Island; Johns Hopkins University School of Medicine, Baltimore, Maryland; Department of Pediatric Psychology, Khute Children’s Rehabilitation Center, University of Virginia, Charlottesville, Virginia; KCRC Pediatric Psychology, University of Virginia, Charlottesville, Virginia; Division of Geographic and International Medicine; University of Virginia School of Medicine, Charlottesville, Virginia; Unidade de Pesquisas Clínicas HUWC/CSCS, Universidade Federal do Ceará, Porangabussu, Fortaleza, CE, Brazil; Division of Geographic and International Medicine and Office of International Health, University of Virginia School of Medicine, Charlottesville, Virginia

Abstract. Diarrhea is well recognized as a leading cause of childhood mortality and morbidity in developing countries; however, possible long-term cognitive deficits from heavy diarrhea burdens in early childhood remain poorly defined. To assess the potential long-term impact of early childhood diarrhea (in the first 2 years of life) on cognitive function in later childhood, we studied the cognitive function of a cohort of children in an urban Brazilian shantytown with a high incidence of early childhood diarrhea. Forty-six children (age range, 6–10 years) with complete diarrhea surveillance during their first 2 years of life were given a battery of five cognitive tests. Test of Non-Verbal Intelligence-III (TONI) scores were inversely correlated with early childhood diarrhea (P = .01), even when controlling for maternal education, duration of breast-feeding, and early childhood helminthiasis (Ascaris or Trichuris). Furthermore, Wechsler Intelligence Scale for Children (WISC-III) Coding Tasks and WISC-III Digit Span (reverse and total) scores were also significantly lower in the 17 children with a history of early childhood persistent diarrhea (PD; P < .05), even when controlling for helminths and maternal education. No correlations were seen between diarrhea rates and Wide Range Assessment of Memory and Learning subtests or WISC-III Mazes. This report (with larger numbers of participants and new tests) confirms and substantially extends previous pilot studies, showing that long-term cognitive deficits are associated with early childhood diarrhea. These findings have important implications for the importance of interventions that may reduce early childhood diarrheal illnesses or their consequences.

INTRODUCTION

Diarrhea in developing countries is a leading cause of child morbidity and mortality and a serious cause and effect of malnutrition. Numerous studies have assessed the effects of early childhood malnutrition (including micronutrient deficiency, anemia, and helminthiases) on cognitive development, but no other studies to our knowledge have specifically addressed the possible long-term impact of early childhood diarrhea (ECD; the number of episodes of diarrhea in the first 2 years of life) on cognitive function in later childhood. Such an effect, as has been shown for intestinal helminths infections for example, would have tremendous importance in helping to demonstrate the potential lasting impact of these common early childhood illnesses and this an even greater urgency for their control.

Since August 1989, we have conducted intensive surveillance for diarrheal diseases and nutritional status among a cohort of children born into an urban Brazilian shantytown. Building on our studies showing long-term associations of ECD with reduced physical fitness and growth, we undertook the current analysis to determine whether ECD burdens on cognitive function in later childhood. Our purpose was to examine whether ECD correlates with reduced cognitive function 4 to 7 years later as assessed by the Test of Nonverbal Intelligence (TONI-III) and other testing and whether early childhood persistent diarrhea (defined as a diarrheal illness lasting 14 days or more) correlates with reduced performances on WISC-III coding tasks and reverse and total digit span and other tasks.

METHODS

All 47 cohort children (27 girls, 20 boys; age range, 6–10 years; mean, 8 years, 2 months ± 10 months SD), who had complete diarrhea surveillance data from their first 2 years of life and who had reached 6 years of age (appropriate for testing) were invited to participate after parental informed consent was obtained. Maternal education was assessed both dichotomously (completion of primary school; i.e., 8th grade or not) as well as continuously (actual number of years of mothers’ schooling; available for 39 of the children). An episode of diarrhea is defined as three or more liquid stools per day separated from other illnesses by at least 2 diarrhea-free days; an episode of persistent diarrhea was defined as an episode lasting 14 days or more. One child declined to participate. The other 46 completed the battery of five cognitive tests, including the Test of Non-Verbal Intelligence (3rd edition; TONI-III); Wide Range Assessment of Memory and Learning (WRAML) subtests: Visual Learning and Delayed Recall; Wechsler Intelligence Scale for Children (3rd edition; WISC-III) Coding; WISC-III Mazes; and WISC-III Digit Span (forward and reverse). Peter D. Patrick, a pediatric neuropsychologist, and Lori L. Derr, a cognitive therapy psychologist, selected the tests and trained Mark D. Niehaus (who was unaware of diarrhea histories) as tester to administer the tests in a standardized manner with instructions in Portuguese. Tests used were standardized psychometric matrix learning tests and an organized memory test, selected for their relative language and culture independence. The TONI-III has been validated in three groups who do not have English as their first language, including comparison studies with...
more than 1,700 Hispanic children who do not have English proficiency as well. In addition, three cohort children, not eligible for this study because of incomplete surveillance data, were selected for pilot testing to confirm that the tests were usable in this setting. Test scores were validated by the child psychologist and converted into scaled, age-appropriate scores wherever possible.

All tests were administered in Portuguese with the aid of a Brazilian health care worker dedicated to this project. The testing location was in a quiet, isolated environment. Total testing time averaged 50 minutes. Each child was tested in two sessions with a 30-minute break in between. The test givers were unaware of children’s illness histories until testing was completed for all children.

RESULTS

The characteristics of the study population are shown in Table 1. The mean number of episodes of diarrhea in their first 2 years of life was 10.2 (± 7.6 SD); only 15% of mothers had completed primary schooling; nearly half had household incomes less than $102 per month. Anthropometry measures are shown.

As shown in Figure 1, TONI-III quotients were associated with the number of episodes of early childhood diarrhea (ECD), even after controlling for maternal education, measured as completion or noncompletion of primary school (8th grade); and for helminthiasis (22 of the 46 children had Ascaris lumbricoides or Trichuris trichiura) during the first 2 years of life \( (P = .049 \) by regression analysis). Only 2 of 18 children tested in the last 12 months before cognitive testing had intestinal helminths. ECD was also significantly associated with reduced TONI-III quotients independent of hemocrits, which were available for 39 of these children. Finally, not surprisingly, a higher level of maternal education (completion of primary school) was positively correlated with the child’s cognitive function, as measured by the TONI-III \( (P = .001) \), even though controlling for this (along with helminths) or for duration of breast-feeding did not remove the correlation of reduced TONI-III scores with early childhood diarrhea. Further refinements of maternal education by actual years of maternal education (available for 39 of these children) also showed a correlation with children’s TONI scores \( (P = .002) \); controlling for actual years of maternal education still left a strong trend of negative correlation of diarrhea episodes with TONI scores \( (P = .075) \).

Table 2 shows the regression analyses of TONI-III scores with early childhood diarrhea, controlling for nutritional status as well as for socioeconomic status and intestinal parasitic infections. Although HAZ was correlated with TONI-III scores \( (P = .01) \), when HAZ and ECD were included in the same model, ECD was slightly more significant than HAZ as a predictor of TONI (for ECD \( P = .09 \) and for HAZ \( P = .110 \)). Neither ECD nor HAZ was a significant \( (P < .05 \) predictor of TONI, independent of the other variable (i.e., ECD was just as good, if not better, a predictor of TONI results as present nutritional status).

Finally, as shown in Figure 2, WISC-III coding task, total digit span, and reverse digit span scores were each signifi-

Table 1

<table>
<thead>
<tr>
<th>Cohort characteristics</th>
<th>No.</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years, months)</td>
<td>–</td>
<td>8 ± 10</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (41%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27 (59%)</td>
<td></td>
</tr>
<tr>
<td>Mean no. early-childhood diarrhea at 0–2 years</td>
<td>46</td>
<td>10.2 ± 7.6</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>46</td>
<td>3275 ± 415</td>
</tr>
<tr>
<td>Nutritional status at time of study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean height-for-age Z</td>
<td>38</td>
<td>0.16 ± 0.9</td>
</tr>
<tr>
<td>Mean weight-for-age Z</td>
<td>38</td>
<td>−0.18 ± 1.4</td>
</tr>
<tr>
<td>Mean weight-for-height Z</td>
<td>36</td>
<td>−0.56 ± 1.3</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below primary school</td>
<td>39 (85%)</td>
<td></td>
</tr>
<tr>
<td>Primary school or above</td>
<td>7 (15%)</td>
<td></td>
</tr>
<tr>
<td>Monthly income*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 1 minimum salary</td>
<td>22 (48%)</td>
<td></td>
</tr>
<tr>
<td>1 minimum salary or above</td>
<td>24 (52%)</td>
<td></td>
</tr>
</tbody>
</table>

*1 minimum wage = US$102/month.

Table 2

<table>
<thead>
<tr>
<th>TONI-III score</th>
<th>R²</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric covariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>.315</td>
<td>.012</td>
</tr>
<tr>
<td>Height for age Z</td>
<td>.267</td>
<td>.129</td>
</tr>
<tr>
<td>Weight for age Z</td>
<td>.301</td>
<td>.091</td>
</tr>
<tr>
<td>Weight for height Z</td>
<td>.236</td>
<td>.046</td>
</tr>
<tr>
<td>Birth weight</td>
<td>.141</td>
<td>.020</td>
</tr>
<tr>
<td>Socioeconomic covariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal education (±1 primary school)</td>
<td>.315</td>
<td>.053</td>
</tr>
<tr>
<td>Monthly income (&lt; or ≥ 1 salary)</td>
<td>.154</td>
<td>.017</td>
</tr>
<tr>
<td>Intestinal parasites at 0–2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptosporidium*</td>
<td>.168</td>
<td>.005</td>
</tr>
<tr>
<td>Giardia†</td>
<td>.168</td>
<td>.058</td>
</tr>
<tr>
<td>Helminths‡</td>
<td>.138</td>
<td>.016</td>
</tr>
</tbody>
</table>

* p is for negative correlation between TONI-III scores and early childhood diarrhea.
† For HAZ n = 42, for WAZ n = 38, and for WHZ n = 36.
Coding and Digit Span, provides a sensitive generalized mea-

surer of overall cortical intellectual capability and concentra-
tion; WRAML and WISC-III mazes, which were not affected, 

more selectively evaluate memory and prospective reasoning.

Although diarrhea, especially persistent diarrhea, is corre-
lated with reduced nutritional status, both early childhood 
diarrhea and nutritional status are independently correlated 
with impaired cognitive function. Although this correlation 
of diarrhea in the first 2 years of life with later reductions in 
cognitive function cannot attribute causality, the huge import-
ance of early childhood years in human brain development 
has been repeatedly emphasized.7–9 Thus, the additive and 
lasting effects of early childhood diarrhea and malnutrition 
are of potential paramount importance in the development to 
full functional capacity. When taken with impaired fitness 
(that correlates in adults with impaired work productivity)10 
and with impaired growth, the additional impact of early 
childhood diarrhea on cognitive function even further mag-
ifies its potential lasting “disability costs.” Furthermore, 
these findings likely represent a “best case” scenario in that 
our long-term follow-up (with its concomitant education 
about breast-feeding, oral rehydration, and treatment of rec-
ognized helminthic infections) has been associated with re-
duced diarrhea rates and improvement in nutritional status 
over the study period.11 effects that we have not seen in 
recently shantytown communities not under study (Lima 
and Guerrant, unpublished observations). Finally, treatment 
of helminth infections has been shown to improve cognitive 
function in Indonesian children aged 6 to 8 years12 and Ja-
mican children aged 6 to 10 years.13 If confirmed in other 
areas, these findings will greatly expand our understanding of 
the DALY impact of early childhood diarrhea and thus the value 
of interventions that reduce these illnesses or their impact.

Future studies should focus on early childhood diarrhea 
and specific cognitive skills, including attention, concentra-
tion, working memory, psychomotor persistence and nonver-
bal reasoning, assessing cognitive function at intervals after 
early childhood diarrhea, and establishing whether a thresh-
old effect exists. Furthermore, despite the relative homoge-
neity of this shantytown population, subtle differences in ma-
ternal education may well (and likely do) influence both di-
arrhea and cognitive development. We have controlled for 
known factors such as recent helminths and anemia. Other 
illness were not sufficiently prevalent to analyze separately; 
no major other illness were identified in these children.

Clearly, more extensive studies are warranted to determine 
the possible mechanisms and implications of these findings 
as well as to assess the cost-effectiveness of interventions to 
avert this potentially huge disability impact.

REFERENCES

severe malnutrition on mental development. J Nutrition 
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