International Journal for Parasitology 42 (2012) 1159–1163

Contents lists available at SciVerse ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara

Reduced cognitive function in children with toxocariasis in a nationally representative sample of the United States

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ARTICLE INFO

Article history:
Received 26 July 2012
Received in revised form 3 October 2012
Accepted 5 October 2012
Available online 1 November 2012

Keywords:
Toxocara
Toxocariasis
Cognitive function
Seroepidemiology

ABSTRACT

Toxocariasis has recently been recognised as a potentially important neglected infection in developed countries, particularly those that experience substantive health disparities such as the United States. Given a relatively high prevalence of infection, an association between *Toxocara* infection and cognitive function may elucidate an important mechanism by which toxocariasis could contribute significantly to morbidity while still remaining hidden and, thus, neglected. To assess the potential relationship between toxocariasis and cognitive function, this investigation measured differences in components of both the Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Wide Range Achievement Test-Revised (WRAT-R) in children seropositive and in children seronegative for *Toxocara* antibodies in the Third National Health and Nutrition Examination Survey, a large, nationally-representative survey of the United States population. Seropositive children scored significantly lower on the WISC-R and WRAT-R compared with the seronegative children. Moreover, this relationship was independent of socioeconomic status, ethnicity, gender, rural residence, cytomegalovirus infection and blood lead levels. These results identify an important association that may reflect morbidity attributable to a genuine neglected infection. Nevertheless, longitudinal data are required to confirm an etiological connection between toxocariasis and cognitive function, as well as the true population attributable risk for toxocariasis and its chronic sequelae.

1. Introduction

Despite adequate health resources, the United States continues to experience significant within-population disparity in health and morbidity (Adler and Rehkopf, 2008). Such disparities are often defined by the socioeconomics of ethnicity and poverty. Moreover, while the contributors to health disparity are multifaceted, neglected communities consistently manifest poorer health due to both chronic and infectious disease. Indeed, the distinctions between chronic and infectious disease may be difficult to distinguish, particularly with respect to the occurrence of what have been referred to as the neglected infections of poverty (Hotez, 2008). Neglected infections of poverty (NIP) are typically chronic infections, which often lead to chronic disease such as asthma, cardiovascular disease and poor cognitive development (Hotez, 2008; Hotez and Wilkins, 2009).

One such NIP in the United States is toxocariasis. It has been suggested that toxocariasis may represent the most important NIP in the United States (Hotez and Wilkins, 2009). Studies based on NHANES III have reported relatively high seroprevalence of *Toxocara* spp. antibodies (Won et al., 2008; Congdon and Lloyd, 2011). While the overall seroprevalence of *Toxocara* infection among all age groups was estimated at close to 14%, there were also marked differences across ethnic groups, with a seroprevalence of 21.2% among African-Americans, 10.7% among Mexican-Americans and 12.0% among Whites (Won et al., 2008). Most *Toxocara* infections are thought to be asymptomatic and acute complications, such as visceral or ocular larva migrans, rare. While acute complicated toxocariasis is indeed rare, this may not be the only relevant clinical presentation. Rather, more insidious chronic disease involving the lungs, vasculature and CNS may be more prevalent than previously expected and, thus, of greater public health significance (Hotez and Wilkins, 2009). With respect to neurological involvement, previous investigations have identified an inverse association between toxocariasis and cognitive function in children, wherein those infected with *Toxocara* spp. demonstrated poorer performance on multiple cognitive assessment instruments (Marmor et al., 1987; Nelson et al., 1996). Nevertheless, these studies were

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0020-7519/$36.00
http://dx.doi.org/10.1016/j.ijpara.2012.10.002

limited by small sample sizes (Marmor et al., 1987; Nelson et al., 1996) and incomplete control of confounding (Nelson et al., 1996).

To explore the possible relevance of toxocariasis as a neglected infection we sought to identify its association with cognitive function in children. This study tested the differences in two cognitive performance examination components between children with and without serological evidence of *Toxocara* spp. infection in a large representative sample of children living in the United States.

2. Materials and methods

2.1. Survey and laboratory procedures

The relationship between *Toxocara* infection and cognitive function among US children was tested using data from NHANES III conducted between the years of 1988 and 1994 by the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC), USA. Methods describing this national survey have been reported previously (National Center for Health Statistics, US Department of Health and Human Services (DHHS). Third National Health and Nutrition Examination Survey, 1988–1994, NHANES III Examination Data File. Public Use Data File Documentation Number 76200. Hyattsville, MD, USA: Centers for Disease Control and Prevention, 1996. Components are available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/nhanes/nhanes3/1A/exam-acc.pdf; ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/nhanes/nhanes3/1A/YOUTH-acc.pdf; ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/nhanes/nhanes3/1A/lab-acc.pdf), but are summarized briefly here. The survey was designed to obtain nationally representative estimates of the health and nutritional status of the population of the United States through personal interviews and physical examinations. Participation in the study was generally good, with 86% response for the questionnaire interview, and 78% response for the examination, which included blood samples subsequently stored and used for the identification of *Toxocara* antibodies. The socioeconomic and demographic data, cognitive testing and laboratory measures were collected in the NHANES Mobile Examination Center (MEC). Antibodies to *Toxocara* spp. were measured at a later date using stored sera from the initial MEC exam with an in-house enzyme immunoassay (EIA) developed at the CDC. This EIA used an excretory/secretory antigen of *Toxocara canis* (Center for Disease Control (2007) Documentation, codebook and frequencies; surplus sera laboratory component: antibody to *Toxocara* larva migrans. NHANES III, series 11 Data Files 26A (ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/nhanes/nhanes3/26a/SSTOXO.pdf).The assay did not distinguish between antibodies against *T. canis* and *Toxocara cati* (Won et al., 2008), so this report simply refers to *Toxocara* spp. infection throughout the text. Cognitive function was measured in children 6–16 years of age using components of two standardized tests. The first was the Wechsler Intelligence Scale for Children-Revised (WISC-R), and the second was the Wide Range Achievement Test-Revised (WRAT-R). The mathematics (math) and reading components of the WRAT-R, and the verbal (Digit Span test) and performance (Block Design test) components of the WISC-R, were used in the NHANES evaluation protocol and are the same components presented here (“NHANES III Examination Data File (catalog Number 76200)” n.d.). Whole blood lead concentration was measured for each child and recorded in μg/dL. The total household income and the poverty:income ratio (PIR) were both used to indicate socioeconomic status. Both were used since household income provides an absolute measure of economic status (in US $1,000 increments), while the PIR is a measure of household income relative to the poverty threshold (in US $) and thus provides a measure of socioeconomic status adjusted for family size and age. Ethnicity was self-reported and grouped into four categories: African-Americans, Mexican-Americans, Whites and Other. The category “Other” was not included in the analyses due to the uncertain designation. Finally, because congenital infection with cytomegalovirus (CMV) may also be associated with cognitive development, and as CMV IgG antibodies were also measured in NHANES III, we further adjusted for infection with this virus in the modeling procedures described in Section 2.2. A total of 3,949 participants aged 6–16 years at the time of examination were tested for the presence of *Toxocara* spp. antibodies and had the WRAT-R and WISC-R administered. Whole blood lead levels were also available for all of these children. This is the analytical sample used for this study.

2.2. Statistical analysis

Sample population means and proportions are presented for descriptive comparisons between those with and those without *Toxocara* infection. Multiple linear regression was used to assess the independent association between *Toxocara* infection and each cognitive function outcome separately (WRAT-R: math, WRAT-R: reading, WISC-R: digit span and WISC-R: block design, respectively) while controlling for gender, ethnicity, income level, PIR, urban versus rural residence, CMV infection and blood lead levels in each of the four models. Because the cognitive tests were evaluated on an age-based standardized scale, age was not additionally controlled for in the models as this would over-adjust for age. A sensitivity analysis was conducted to identify the potential for reverse causality in the cross-sectional associations observed in this study. To rule out the possibility of congenitally mentally disabled children being over-represented among children with toxocariasis, we reran each of the four models described above, including only those children who scored equal to or greater than the median score for each of the four cognitive function tests. The sensitivity analysis yielded no differences in the regression coefficients in substance or significance, so the models including all eligible children were preserved and are presented below. The svymean, svyprop and svyregress (for the linear regression models) commands in Stata were used in order to account for the NHANES weighted sampling design. Although specific *P*-values are presented, the level of significance was considered to be 0.05. Stata (version 11) was used for all statistical analyses (StataCorp LP, College Station, TX, USA).

3. Results

The overall prevalence of previous *Toxocara* infection among children aged 6–16 years in the NHANES III was 13.4%. Differences in sociodemographics, risk factors and measures of cognitive function are presented in Table 1. All four measures of cognitive function in math ($P < 0.001$), reading ($P < 0.001$), the block design performance ($P < 0.001$), and the verbal digit span ($P < 0.001$), were significantly reduced in children with previous *Toxocara* infection. The mean math and reading scores from the WRAT-R were 1.68 points and 1.58 points lower, respectively, among those with evidence of toxocariasis, while the mean block design and digit span scores from the WISC-R were 1.49 and 0.83 points lower, respectively, again among infected children. Infected children were, on average, only slightly older (0.72 years), although this difference was significant. The household income was $4,000 less ($P < 0.001$) and the PIR 0.8 less ($P < 0.001$) among *Toxocara*-infected children. African-American children had the highest *Toxocara* seroprevalence at 22.8%, followed by Mexican-Americans at 12.6%, and Whites at 10.6%. These ethnic differences in seroprevalence were significant ($P < 0.001$). There was no meaningful difference in prevalence between boys and girls, however, there was a somewhat higher *Toxocara* prevalence in rural residents (14.7%) compared