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Developmental Outcomes in Young Children Born to Mothers with West Nile Illness during Pregnancy

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Abstract

Background—West Nile virus (WNV) infection is associated with acute morbidity and mortality in adults and children. Information on the effects of maternal WNV illness during pregnancy on early childhood development is limited. This study was designed to examine the relationship between maternal WNV illness during pregnancy and birth and developmental outcomes at age 3 years.

Methods—Mother-child participants were identified using a national surveillance registry for women with WNV illness during pregnancy. Maternal and infant health data and relevant family characteristics were obtained through medical record reviews and maternal questionnaires. All infants received ophthalmologic examinations. Child development was evaluated at age 3 years using the Bayley Scales of Infant and Toddler Development—Third Edition (Bayley-III).

Results—As a group, the children's ($N = 11$) birth weight, head circumference, and infant ophthalmologic examination results were within age expectations; one child was born preterm (gestational age 36 weeks). Mean (SD) age at the time of Bayley-III testing was 36.7 (3.8) months. The group's mean performance on the Bayley-III was at or above age level in all domains, but one child showed a mild delay in the Adaptive domain. The variability observed in this sample (1/53 [1.9%] Domain scores < -2.0 SDs) was consistent with expectations based upon the distribution of Bayley-III Domain scores in the general population.

Conclusion—Maternal WNV infection does not appear to be associated with global developmental delays in young children. These results are preliminary, however, and require confirmation in future research.

Keywords

West Nile virus; pregnancy; infancy; early childhood development

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Introduction

West Nile virus (WNV) is a neurotropic virus transmitted primarily through infected mosquitoes but also by means of blood transfusion, organ transplantation, intrauterine exposure, and in laboratory settings (Hayes and O'Leary, 2004; Lindsey et al., 2010). Although the majority of individuals infected with WNV are asymptomatic, approximately 20% develop WNV illness manifested by fever, headache, myalgias, and other nonspecific symptoms, and approximately 1% develop neuroinvasive disease such as meningitis, encephalitis, or acute flaccid paralysis (Petersen and Marfin, 2002; Hayes and O'Leary, 2004; Hayes et al., 2005; Carson et al., 2006; O'Leary et al., 2006; Sejvar, 2007). According to the Centers for Disease Control and Prevention (CDC, 2013), the number of reported cases of WNV disease in the United States in 2012 was the highest since 2003, including 2873 (51%) cases classified as neuroinvasive disease and 2801 classified as nonneuroinvasive disease. There were 2469 cases in 2013; as in 2012, half (51%) were classified as neuroinvasive disease (Lindsey et al., 2014).

The first case of congenitally acquired WNV was identified in 2002 (CDC, 2002; Alpert et al., 2003). The mother developed WNV encephalitis at 27 weeks of gestation. Her full-term newborn had laboratory evidence of WNV infection, chorioretinitis, and cystic destruction of cerebral tissue. Subsequently, the CDC established a national WNV Pregnancy Registry in 2003 and produced guidelines for evaluation of potentially infected newborns in 2004 (CDC, 2004). Early analyses of registry data suggested that maternal WNV infection during pregnancy did not commonly cause adverse effects on fetal and newborn growth and development (O'Leary et al., 2006), although long-term outcomes were not evaluated.

Because WNV is neurotropic and able to cross the placental barrier, we hypothesized that prenatal exposure to WNV might increase the risk of developmental delay in young children. The purpose of the present study was to evaluate developmental outcomes of young children born to women enrolled in the CDC's WNV Pregnancy Registry.

Materials and Methods

PARTICIPANTS

There were 72 live births in 2003 to 2004 among women enrolled in the registry (O'Leary et al., 2006). All of the infants were born to women with laboratory-confirmed WNV infection during their pregnancy. All of these mother-child pairs were considered eligible for participation in the study. The mothers were contacted by state or CDC WNV coordinators to request permission for telephone contact from a study investigator at Tulane University. If they agreed, the investigator called the mother to describe the purpose of the study, obtain oral consent to participate, and obtain an address to mail the written informed consent and maternal self-report questionnaire. The call was conducted using a scripted telephone interview. The study was approved by the Institutional Review Boards (IRBs) of Tulane University and the CDC.

PROCEDURES

The present study used information available in the WNV registry, including information from mothers and health care providers about maternal and infant health at delivery and infant health at ages 2, 6, and 12 months. Evidence of maternal WNV infection was ascertained through IgM and IgG ELISA testing of maternal serum, cord blood, placental tissue, umbilical cord tissue, and breast milk obtained at the time of delivery. Follow-up testing of infant serum or cerebrospinal fluid was performed during infancy when clinically indicated (O'Leary et al., 2006). Ophthalmologic examinations were arranged for all infants.

Abstraction of infant and maternal medical records was performed by local physicians and nursing staff and recorded on study-specific data collection forms. For infants, the following information was obtained from physical examinations performed between birth and 42 months of age: evidence of WNV infection (obtained from tests performed during infancy for the WNV Pregnancy Registry), date of birth, sex, gestational age, birth weight and length, head circumference, Apgar scores, temperature at birth, and presence of congenital abnormalities, chorioretinitis, skin rashes, pneumonia, seizures and other neurologic abnormalities, and any other illnesses present at birth and up to 42 months of age. Sex-specific intrauterine growth curves (Olsen et al., 2010) were used to determine the appropriateness for gestational age of the infants' birth weight and head circumference measurements. The following information was abstracted from the mothers' medical records: trimester of infection with WNV, date of onset of symptoms, severity of symptomatic WNV illness (fever vs. neuroinvasive disease), maternal age at delivery, delivery method, temperature and clinical status at delivery, and history of maternal illness, complications of pregnancy, and fetal abnormalities.

The maternal self-report questionnaire was returned by mail to the Tulane investigator. It requested the following information: level of maternal education, occupation, race/ethnicity, marital status, household income, family history of birth defects, history of maternal illness during pregnancy, and history of use of medications, tobacco, and alcohol during pregnancy. Mothers also provided a general description of their perception of their infant's health (sicker than average, average, or very healthy) and development (whether normal or above average).

The Bayley Scales of Infant and Toddler Development—Third Edition. (Bayley-III; Bayley, 2006) were administered to children at approximately 3 years of age by local participating psychologists, using standardized assessment procedures. The evaluations were performed in local clinics or, in one case, in the child's home. The Bayley-III provides standardized measures of child development in five domains: Cognitive (problem-solving), Language (receptive and expressive skills), Motor (fine- and gross-motor skills), Social-Emotional (social behavior and self-regulation), and Adaptive Behavior (for example, communication, self-care, and pre-academic skills). The Cognitive, Language, and Motor domains are assessed through direct testing with the child; the Social-Emotional and Adaptive Behavior domains are assessed through interviews with the parent. The standardization sample of the Bayley-III provides the reference mean for the Domain Composite scores (Mean = 100, standard deviation [SD] = 15).

Results

The Tulane investigator received contact information for 61 women enrolled in the WNV Pregnancy Registry in 2003 to 2004. Of these, 15 agreed to participate with their children. Seven women declined to participate, and 39 were considered lost to follow-up because their state health department could not locate them. The investigators did not ask the women for their reasons for declining, per IRB guidelines, and study personnel did not have access to demographic or other data about the women and infants who did not participate. When compared with the original cohort (O'Leary et al., 2006), the subset of women who participated in this study were generally older and more predominantly white, non-Hispanic. Of the 15 children enrolled, 11 completed the Bayley-III. Four children missed the assessment due to lack of a qualified local examiner ($n = 1$), missed appointments ($n = 1$), and loss to follow-up (could not be located; $n = 2$).

The mean age of the 11 children at the time of the Bayley-III assessment was 36.7 (SD = 3.8) months. According to infant IgM levels at the time of delivery, none of the children were congenitally infected with WNV. The study sample was too small for formal hypothesis testing; descriptive data are presented in Tables 1 and 2.

Relevant health and demographic characteristics of the mothers and children are shown in Table 1. One child was born preterm (gestational age 36 weeks). No child was born at low birth weight; all weighed more than 2500 g. Birth weights and head circumferences were appropriate for gestational age for all infants except two who were large for gestational age (above the 90th percentile), one in birth weight and the other in head circumference. The results of infant ophthalmologic examinations were within normal limits. Most (64%) of the mothers had at least a college degree, and 82% had annual household incomes greater than \$40,000. Most (82%) of the mothers were infected with WNV during the second or third trimester. The mothers' responses to the self-report questionnaire, completed 3 to 16 months before infant testing, indicated that 55% perceived their infants' health as "average," and 64% perceived their infants' overall development as "normal" (Table 1).

As a group, the children's performance was at or above age level in all domains of the Bayley-III (Table 2). One child was in the mildly delayed range in the Adaptive Behavior domain but at age level on the Cognitive, Language, Motor, and Social-Emotional domains. The local examiner attributed this child's lower Adaptive score to lack of environmental opportunity rather than to developmental delay. Most of the mothers in the study ($n = 9$; 82%) had nonneuroinvasive WNV illness. Two mothers (18%) had meningitis, indicating the presence of neuroinvasive WNV disease; there was no evidence of developmental delay in their children's performance on the Bayley-III.

Discussion

The findings of the present study were consistent with previous studies of infants born to women with WNV infection (O'Leary et al., 2006; Ornoy and Tenenbaum, 2006), indicating that maternal WNV illness during pregnancy does not commonly cause global developmental delay in young children. As a whole, the children in this study performed

within age expectations in all developmental domains assessed at age 3 years. In addition, they were medically well at birth and at repeated follow-up examinations with their local medical providers during the first 3 years of life. One child demonstrated lower-than-expected performance in one domain but did not show evidence of a global delay in development.

The strengths of this study include the long-term follow-up and standardized assessment of child development. This analysis provides additional information on development for a subset of infants previously described at age 12 months by O'Leary and colleagues (O'Leary et al., 2006). At an evaluation at 3 years of age, we did not find evidence of global developmental delay. The study was limited, however, by the small sample size, the lack of a comparison group (beyond the standardization sample of the Bayley-III), and the demographic homogeneity of the sample. Maternal education and family income are related to child development (Brooks-Gunn and Duncan, 1997; Bradley and Corwyn, 2002). It is possible that mothers who participated in the study had greater resources available to them than mothers who did not participate, and these resources may have protected the children from the potentially adverse effects of prenatal exposure to WNV. The study was also affected by logistical difficulties such as geographical distance to the study sites and limited access to qualified examiners for the Bayley-III assessment. These factors may have introduced a selection bias by increasing the burden of research participation for parents enrolled in the study and for those who chose not to enroll. We did not test infants for WNV infection after birth; it is possible that an infant's results may have been influenced by WNV infection acquired between the time of delivery and the time the developmental assessments were performed.

To our knowledge, this study is the first of its kind, and the findings warrant confirmation in future research. Although the results were reassuring, the number of children we were able to evaluate, despite intensive effort, was small. A prospective study of infants born to women enrolled in the WNV Pregnancy Registry is underway. Data from the medical examinations and developmental assessments obtained in that study will provide additional information about the developmental outcomes of children born to mothers with WNV infection during pregnancy.

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TABLE 1Health and Demographic Characteristics of Study Participants ($N = 11$).

	Characteristic	Mean (SD) or n (%)	
Infant	Gestational age (weeks)	38.3 (1.2)	
	Birth weight (g)	3200 (400)	
	Head circumference (cm)	35.0 (1.0)	
	Vaginal delivery	5 (45%)	
	Caesarean delivery	5 (45%)	
	Congenital abnormality present ^a	4 (36%)	
	Age at Bayley-III assessment (months)	36.7 (3.8)	
Maternal	Age at delivery (years)	34.0 (4.7)	
	Education: college degree or higher	7 (64%)	
	Caucasian race/non-Hispanic ethnicity	11 (100%)	
	Trimester of infection: first, second, third	2 (18%), 5 (46%), 4 (36%)	
	Complications of pregnancy present ^b	4 (36%)	
	Reported smoking during pregnancy ^c	0	
	Alcohol use during first 20 weeks of pregnancy ^c	2 (18%)	
	Household income above \$40,000 per year ^d	9 (82%)	
	Perception of infant's health:		
	Sicker than average	0 (0%)	
	Average	6 (55%)	
	Very healthy	5 (45%)	
	Perception of infant's development:		
Normal	7 (64%)		
Above average	4 (36%)		

^aTwo women had a newborn with a major birth defect (cleft palate and aortic coarctation); however, both women were infected with WNV in the third trimester, presumably after the abnormality had developed.

^bComplications reported by mothers' physicians included hypertension, chorioamnionitis, severe yeast infection, and severe preeclampsia; none were considered likely to have had an adverse effect on the infants' development.

^cThree women chose not to respond to this item.

^dOne woman chose not to respond to this item.

TABLE 2

Bayley-III Domain Composite Scores

ID	Age at Testing (months)	Domain				
		Cognitive	Language	Motor	Social-Emotional	Adaptive
R1	40	105	115	107	105	103
R2	36	95	100	107	100	67
R3	36	110	109	100	125	105
R4	27	100	89	82	105	93
R5	37	105	112	94	140	115
R6	39	135	112	115	n/a	150
R7	37	120	118	97	105	115
R8	42	145	121	142	n/a	120
R9	35	115	94	107	110	116
R10	36	105	118	103	125	125
R11	39	105	115	110	140	112
Group Mean (SD)	36.7 (3.8)	112.7 (15.2)	109.4 (10.5)	105.8 (15.0)	117.2 (15.6)	111.0 (20.5)

The mean (\pm SD) of the Bayley-III standardization sample (reference mean) is 100 (\pm 15) for Domain Composite scores. n/a = score not available.