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Findings of Long-Term Depression up to 8 Years Post Infection From West Nile Virus

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Abstract

Objective—To examine the psychological sequelae following West Nile virus (WNV) infection among a large cohort of participants over an 8-year period.

Design—We conducted a longitudinal study to assess mental health outcomes among a cohort of 171 WNV-positive participants in Houston, Texas.

Results—We found 35% of participants met the Center for Epidemiologic Studies Depression scale definition for new onset clinical depression. Multivariate analysis found that severe depression was significantly associated with gender and physical disability (Barthel index score <100) at 5 years post-WNV infection.

Conclusions—Practitioners should be aware of depression as a possible outcome in patients who were infected with WNV and include this as a part of their routine assessment.

Keywords

depression; West Nile virus; Barthel index; Center for Epidemiologic Studies Depression (CESD) scale; long-term outcomes; longitudinal study

West Nile virus (WNV) was first identified in North America in 1999 during an outbreak in New York City. Since the initial outbreak, WNV has rapidly spread across the continental United States and has recently become endemic in most states (Nash et al., 2001; Centers for Disease Control and Prevention [CDC], 2006). From its establishment in North America until 2010, the Centers for Disease Control and Prevention Arbonet surveillance system has identified 30,702 symptomatic cases, including 1,220 deaths (CDC, 2011). Based on the number of reported cases, an estimated 1.8 million Americans have been infected with WNV since its introduction in 1999.

The majority (approximately 80%) of people infected with WNV do not develop symptoms of disease, while approximately 20% of individuals develop febrile disease. Less than 1% develops neuroinvasive disease, which is characterized as encephalitis, meningitis, and/or acute flaccid paralysis (Mostashari et al., 2001). Several studies have noted continued

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physical, cognitive, and functional problems in patients post WNV infection (Voelker, 2008; Loeb et al., 2008; Klee et al., 2004; Carson et al., 2006; King et al., 2007). Half of participants with mild to moderate disease and 60% of participants with severe disease continue to report symptoms after 1 year (Voelker, 2008). Long-term neuropsychological outcomes of disease have similar morbidity rates among all groups of disease severity (Carson et al., 2006). While morbidity rates are similar among disease severity groups, it is believed that those with neuroinvasive disease are at a higher risk for developing severe depression (Berg, Smallfield, & Svien, 2010).

Depression has been documented as one prominent neuropsychological outcome reported by patients (Klee et al., 2004; Murray, Resnick, & Miller, 2007). One year after initial infection, 31%–38% of participants reported depression as a continued symptom of their WNV disease (Klee et al., 2004; Murray et al., 2007). It is speculated that these rates underestimate the true proportion of patients with chronic psychological and cognitive problems. Researchers in New Mexico noted that self-reporting of subjective mental deficits was marginally associated with validated objective mental scores (Haaland et al., 2006). Their findings suggest self-reporting to be an unreliable measure of true cognitive problems, especially among those with neuroinvasive WNV disease. Therefore, research is needed to better objectively measure and understand the role of depression as a long-term outcome following WNV infection. This study aimed to longitudinally examine rates and levels of depression using both subjective and validate objective measurements among a cohort of study participants post WNV infection.

Methods

Participants

In 2003, a cohort of study participants with a recent history of WNV infection was established at the University of Texas Health Science Center at Houston. Potential participants were identified through regular surveillance conducted by the Houston Department of Health and Human Services, Harris County Public Health and Environmental Services, or the Gulf Coast Regional Blood Center. A few participants contacted the study independent of these organizations for personal enrollment into the study. Participants were eligible if they tested positive by an accredited laboratory for either IgG and/or IgM antibodies by enzyme-linked immunosorbent assay, or for viral ribonucleic acid by real-time polymerase chain reaction. Since the cohort's inception, 182 study participants have been consented and enrolled. Of those eligible, interviews from 171 study participants contributed to this analysis. The 11 study participants that did not take part were determined ineligible due to death, repeat lab results indicated a false positive case, ruled a lost-to-follow-up case, or personal choice to no longer participate. Case classification was established based on their acute clinical presentations and the CDC guidelines (CDC, 2008). Participants with neuroinvasive disease were defined as those who presented with encephalitis, meningitis, and/or acute flaccid paralysis. Participants with non-neuroinvasive disease were defined as those presenting with uncomplicated febrile illness or no symptoms. This study was reviewed and approved by the University of Texas Health Science Center Institutional Review Board (HSC-SPH-03–039).

Measurements and Materials

Questionnaires used in participant interviews included subjective and objective measurements. Participants were asked to report if they continued to experience any symptoms related to their initial WNV disease, if currently suffering from depression, and if a history of depression prior to WNV infection. Participants were also asked to report their date of birth, sex, and gender. Objective measurements assessed mental health and physical functioning by two validated assessments: Center for Epidemiologic Studies Depression scale (CES-D) and the Barthel index. The CES-D scale included 20 questions, scored 0–3, which evaluated various depressive symptoms and the severity participants might have felt over the past week (Pandya, Metz, & Patten, 2005). The Barthel index measured a participant's physical level of functioning by asking a series of questions related to everyday activities and the participant's ability to perform them (Shah, Vanclay, & Cooper, 1989). Scores ranged from 0–100, with 100 being fully physically independent, and scores less than 100 indicating being unable to perform a physical task or needing assistance.

Procedure

Study participants took part in biannual interviews between May 2003 and November 2010. Trained research staff conducted the interviews using the questionnaires previously mentioned. Study participants were assessed for depressive symptoms using the CES-D scale. Scores were totaled and ranged from 0–60. Using the CES-D scores, depression was evaluated two ways. First, scores of 16 or higher indicated the presence of clinically significant depression. To further refine the severity of depression, we defined mild to moderate depression as a CES-D score of 16–23, and severe depression as CES-D score of 24 or greater (Munoz, 2005). The Barthel index was used to investigate the influence of physical disability on depression.

Interviews were grouped according to follow-up year for purposes of this study. Follow-up interview year was calculated by subtracting date of interview from date of onset. An imputation method was used for asymptomatic cases without a classified date of onset. We used the first of August of the year of their diagnosis from the blood bank or other clinical institution as their onset date. Since the majority of cases in Houston, TX occurred in August, this was determined appropriate (CDC, 2006). Years were grouped by whole integers with ranges of +/− 0.49 years for years 1–8 after initial infection. If participants had more than one interview within 1 year, the interview closest to the year integer was included and any other interviews were excluded. While this decreased the sample size, our main focus was to look at symptoms at disease anniversary versus throughout the continuous year.

Descriptive statistics were performed for all variables assessed. As a way to determine the relationship between subjective reporting of depression and an objective measurement of depression, we conducted a Kruskal-Wallis one-way analysis of variance (ANOVA) on ranks analysis. Linear regression was performed to evaluate change in CES-D scores over time by neuroinvasive WNV disease status. Using the objective depression measure, CES-D, we conducted a univariate logistic regression between potential risk factors for depression and the presence of depression (CES-D ≥16) and severe depression (CES-D ≥ 24). All variables

with $p < 0.25$ from univariate analysis were subjected to multivariate analysis. A backward stepwise approach eliminated variables with $p > 0.10$.

Results

Interviews from 171 study participants contributed to this analysis. Of those who participated, 59% had neuroinvasive WNV disease, 61% were male, and the average age at acute infection was 51 years with a range of 9–99. Participants were 81% non-Hispanic White, 7% Hispanic White, 12% non-Hispanic Black, and >1% Asian. Table 1 includes the findings of each subjective and objective measurement according to follow-up year. Over the 8-year follow-up period, an average of 70% of participants continued to experience symptoms related to their acute WNV infection, and an average of 55% of participants reported suffering from current depression at the time of follow-up. When looking at new onset depression, an average of 39% of participants self-reported experiencing depression, compared with an average 35% were found to meet the CES-D definition for depression.

At both Year 1 and Year 5 postinfection, self-report of experiencing depression was statistically associated with an elevated CES-D score (Kruskal-Wallis ANOVA on ranks, Year 1: chi-square = 32.5, $p < 0.001$; Year 5: chi-square = 15.0, $p < 0.001$), indicating comparable findings between subjective reporting and objective measurements at both year time points. Linear regression of CES-D scores overtime grouped by neuroinvasive disease status found no statistical significance. This finding suggested no significance difference of CES-D score change overtime between those with a history of neuroinvasive WNV disease compared with those with a history of febrile, mild or asymptomatic WNV disease.

Results from univariate logistic regression are shown in Table 2. Presence of depression (CES-D≥16) was not significantly associated with any risk factors at Year 1 postinfection; however, at Year 5 postinfection, presence of depression was significantly associated with gender ($p = 0.006$) and having a Barthel index score of less than 100 ($p = 0.049$). Presence of severe depression (CES-D≥24) was significantly associated with gender ($p = 0.053$) at Year 1 postinfection and at Year 5 postinfection ($p = 0.025$), and having a Barthel index score of less than 100 ($p = 0.038$) at Year 5 postinfection. All significant associations of depression and severe depression with gender were protective (odds ratio [OR] range: 0.11 – 0.26), indicating that females are more likely to suffer from depression than males. Both significant associations between Barthel index scores less than 100 indicated increased odds of depression (OR range: 4.17 – 6.18) among those with impaired physical functioning.

Table 3 lists the significant results from multivariate regression between risk factors and severe depression (CES - D ≥ 24). At 1-year post-WNV infection, severe depression was significantly associated with gender ($p = 0.034$), neuroinvasive WNV disease ($p = 0.048$), and having a Barthel index score less than 100 ($p = 0.033$). At 5 years post-WNV infection, severe depression was significantly associated with gender ($p = 0.047$) and having a Barthel index score less than 100 ($p = 0.072$). Interestingly, neuroinvasive WNV disease did not achieve statistical significance until after the multivariate analysis. A clinical presentation of neuroinvasive WNV disease was protective (OR = 0.15) against severe depression at 1-year

postinfection. Odds ratios for gender and Barthel score were consistent with univariate findings.

Discussion

We followed a large cohort of WNV survivors up to 8 years postinfection to monitor their long-term neuropsychological outcomes. We found a high proportion of participants continuing to report symptoms related to their WNV illness (range 59%–85%) several years after acute infection. Additionally, we found a higher than expected proportion of participants with no prior history of depression exhibiting mild to severe depression (range 21%–56%). History of depression before WNV infection was low among this population (8–27%). We show that participants are continuing to report symptoms, especially depression, several years after their infection, and that clinical presentation or disease severity does not determine the outcome of having depression.

The majority of literature has indicated that initial WNV diagnosis is not associated with development and/or severity of physical or mental outcomes; however, one study has found contradictory results (Loeb et al., 2008; Carson et al., 2006; Sejvar et al., 2003; Berg et al., 2010). A study analyzing long-term neuropsychological outcomes suggested that based on their findings nonhospitalized cases might have developed subclinical encephalitis since their rates of outcomes were similar to those of hospitalized cases (Carson et al., 2006). Another study found that patients with a history of febrile WNV had a high incidence of cognitive problems (Haaland et al., 2006). Researchers felt that this was a result of undiagnosed neuroinvasive disease within this population (Haaland et al., 2006).

We found that at 1-year postinfection non-neuroinvasive cases were statistically more likely to suffer from severe depression. If patients with a history of febrile WNV have undocumented neurologic complications, then they might be less likely to seek follow-up medical care potentially resulting in untreated sequelae. This finding was peculiar in that it never achieved univariate significance; it was found to be significant only by the multivariate model at Year 1 for those with severe depression. Neuroinvasive disease status did not have any statistical findings with having mild to moderate depression. We also found that change in CES-D scores over time were not significantly different between the two disease severity groups. While we cannot rule out the influence of neuroinvasive disease on developing severe depression, our findings support that WNV disease severity does not affect the presence of depression after acute infection.

We found that physical disability (as determined by having a Barthel index of <100) and female gender were correlated with severe depression. Physical disability has been found to be associated with major depression in a number of other studies (Naismith, Longley, Scott, & Hickie, 2007; Kim et al., 2005). Naismith, Longley, Scott, and Hickie (2007) found depression severity to be a strong predictor of functional disability. In a study of older Korean individuals, disability was significantly associated with depression (Kim et al., 2005). Our findings of disability and depression appear to be consistent with the literature. In regards to our finding of females being more likely to experience severe depression, we are the first to report these findings. We are unclear as to the physiological cause of this

association, although it is of clinical importance to note that females with a history of WNV are more likely to suffer from severe depression after acute infection.

One main limitation in this study was the potential for selection bias. It is likely that participants who are continuing to experience symptoms are more willing and interested in participating in biannual follow-ups, which could bias the data. In an effort to increase involvement of study participants from all disease severity groups and recovery spectrums, we used monetary incentives considered appropriate by the institutional review board for all participants and emphasized the importance of their participation. It is also possible that we misclassified those with depression and severe depression. We based our main findings on validated measurements and used subjective as supplementary information. While another study found discord between diagnosis methods, we found that subjective reports were as accurate as objective measures at determining true rates of morbidity (Haaland et al., 2006). Our data suggest that discussing depression with a patient is as effective as using a validated measurement for diagnosing depression.

The main strength of this study was the ability to longitudinally track a substantial number of individuals up to 8 years postinfection. We found depression to be prevalent and consistent among our cohort. Physicians should be aware that all WNV survivors are at risk of developing depression. Physicians should regularly discuss depressive symptoms or use a validated measurement tool as part of their mental health assessment. Physicians should be especially aware that females and those without full physical independence are most likely to suffer from severe depression several years after acute WNV disease.

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Table 1

Subjective and Objective Outcomes Among WNV Subjects Over 8 Years Postinfection

	Years postinfection							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
No. interviews	71	45	55	34	38	32	23	16
Persistent WNV-related symptoms at follow-up evaluation, n (%)”	47(66)	29 (64)	37(67)	29(85)	29(76)	19(59)	17(74)	12(75)
Self-reported current depression, n (%)	31(44)	25(56)	32(58)	16(47)	25(66)	15(47)	17(74)	11(69)
History of depression before WNV, n (%)	14(20)	5(11)	14(25)	3(9)	7(18)	3(9)	4(17)	1(6)
Median Barthel Index score (range)	100 (5–100)	100 (5–100)	100 (65–100)	95 (30–100)	99 (55–100)	96 (65–100)	98 (80–100)	98 (80–100)
Median CES-D (range)	9 (0–45)	15 (0–44)	13 (0–39)	9 (0–48)	12 (0–43)	8 (0–47)	10 (0–45)	16 (0–42)
New onset depression[a], CES-D ≥16 (%)	12/57 (21)	15/40 (38)	23/41 (56)	10/31 (32)	11/31 (35)	8/29 (28)	5/19 (26)	7/15 (47)
New onset severe depression[a], CES-D >24 (%)	6/57 (11)	5/40 (13)	8/41 (20)	4/31 (13)	7/31 (23)	2/29 (7)	2/19 (21)	3/15 (20)

WNV= West Nile virus; CES-D = Center for Epidemiologic Studies Depression scale.

[a]Excludes those with a prior history of depression.

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Table 2

Univariate Logistic Regression of Risk Factors and CES-D Defined Depression at Years 1 and 5 Post-WNV Infection (PI)

	Year 1 PI (n=71)		Year 5 PI (n=38)	
	CES-D Score≥16 p-value, OR (95% CI)	CES-D Score≥24 p-value, OR (95% CI)	CES-D Score≥16 p-value, OR (95% CI)	CES-D Score≥24 p-value, OR (95% CI)
Caucasian race	0.616 1.43 (0.35–5.81)	0.889 1.125 (0.21–5.90)	0.415 2.60 (0.26–25.93)	0.732 1.50 (0.15–15.28)
Male gender	0.563 0.73 (0.25–2.13)	0.053 0.26 (0.07–1.01)	0.006 0.11 (0.02–0.53)	0.025 0.14 (0.02–0.78)
Neuroinvasive WNV disease	0.519 0.67 (0.19–2.29)	0.188 0.39 (0.10–1.58)	0.204 0.41 (0.10–1.62)	0.320 0.47 (0.11–2.06)
Age 55+	0.655 1.27 (0.44–3.68)	0.223 0.44 (0.12–1.65)	0.091 0.27 (0.06–1.23)	0.156 0.29 (0.05–1.61)
Barthel Index Score < 100	0.131 2.36 (0.77–7.22)	0.186 2.44 (0.65–9.18)	0.049 4.17 (1.00–17.31)	0.038 6.18 (1.10–34.70)

Note. WNV= West Nile virus; CES-D = Center for Epidemiologic Studies Depression scale; OR = odds ratio, CI = confidence interval.

Table 3

Multivariate Logistic Regression of Risk Factors and Severe Depression (CES-D≥24) at Years 1 and 5 Post-WNV Infection (PI)

	Year 1 PI p-value, OR (95% CI)	**Year 5 PI p-value, OR (95% CI)**
Caucasian race	–	–
Male gender	0.034 0.21 (0.05–0.89)	0.047 0.16 (0.03–0.97)
Neuroinvasive WNV disease	0.048 0.15 (0.02–0.98)	–
Age 55+	–	–
Barthel Index Score < 100	0.033 7.43 (1.17–47.17)	0.072 5.30 (0.86–32.69)

Note. WNV= West Nile virus; CES-D = Center for Epidemiologic Studies Depression scale; OR = odds ratio, CI = confidence interval.