Author's response to reviews

Title: Prognosis of West Nile Virus Associated Acute Flaccid Paralysis: A Case Series

Authors:

Jennie Johnstone (johnsj48@mcmaster.ca)
Steven Hanna (hannas@mcmaster.ca)
Lindsay Nicolle (LNicolle@exchange.hsc.mb.ca)
Michael Drebot (Mike.Drebot@phac-aspc.gc.ca)
Binod Neupane (binodn@gmail.com)
James Mahony (mahonyj@mcmaster.ca)
Mark Loeb (loebm@mcmaster.ca)

Version: 3 Date: 25 April 2011

Author's response to reviews: see over
April 25, 2011

Dear JMCR Editorial Team,

Thank you for giving us the opportunity to revise and resubmit our manuscript entitled, “Prognosis of West Nile Virus Associated Acute Flaccid Paralysis: A Case Series” (MS: 4429529750551201). Our responses to the Reviewers’ suggestions are as follows:

**Reviewer 1**

1. *This is an important case series, as little is known about the prognosis of patients with acute flaccid paralysis due to West Nile Virus infection. The authors propose to improve the understanding of the natural history of this disease (p. 3, paragraph 2). This case series may not reflect the natural history of this disease, which presumes no treatment. There is no information presented on the physical (eg, PT and OT) and psychological (eg, psychotherapy, antidepressants) rehabilitative treatments of these patients, which may have greatly influenced the patient outcomes reported.*

We have removed the word ‘natural’ from the statement mentioned by Reviewer #1 and it now reads as follows: “Improved understanding of the history of this disease, including its impact on health related quality of life is necessary to provide information addressing prognosis for patients at the time of diagnosis” (Page 3, Line 16). We have also added data on use of physiotherapy, occupational therapy and antidepressants for each patient in Table 1.

2. *Of the cohort of 7 patients, 2 should not be included in the analysis. Patient #6 has Parkinson’s disease, which has its own effect on motor and cognitive abilities and which will therefore confound any PCS/MCS scales. This is most evident when observing the trend of PCS and MCS scores, which for this patient was -33 for PCS (baseline 57 - 2 year f/u 24 = 33) and +38 for MCS (baseline 12 - 2 year f/u 50 = 38), the largest trend changes for any patient in the series. Additionally, the baseline MCS of 12 is so far from mean (>3 SD), emphasizing the likelihood that this patient is an outlier. Patient #3 should also not be included in the analysis, as there is no trend to follow, with only 1 PCS/MCS score during the study time. It appears the authors added the scores at baseline and last follow up (pt #3 with only 1 score; all other pts with last follow up at 6 months (3), 1 year (2, one of these being pt #3) and 2 years (2, one of these 2 being pt #6) to achieve the mean PCS and mean MCS score. A trend analysis of the change in score over time provides more meaningful information. Viewing this trend analysis over time, it is apparent there is sometimes very different about patients 1 and 2; perhaps only UE involvement has a better prognosis, perhaps these patients had different rehabilitative therapies, perhaps less impairment at onset=improved scores over time? It is also clear patient 6 is quite different from the other patients, and the Parkinson's disease is very suspect as a confounder. Including only patients 1,2,4,5,7 and only the follow up times that included all patients (baseline, 3 months, 6 months) yields the following table of change over time for mean PCS/MCS. Baseline 3 months 6 months PCS 30 38 46 MCS 38 51 54 This trend analysis yields a baseline PCS of 30 (vs the author's mean presentation PCS score of 35), and a dramatically increased mean PCS of 46 at end of follow up of 6 months (vs the author's mean PCS score at variable follow up of 39) and continued normalization of the MCS.*
We value the Reviewer’s suggestions regarding the results. We have made the following changes:

a) We agree that Patient #6 may confound the results given their history of Parkinson’s disease. We were however, reluctant to begin excluding data post hoc. Instead, we chose to exclude the data from Patient #6 in the mean calculations as a sensitivity analysis (Page 5, Line 18). The exclusion of Patient #6 from the results did not change our main finding, namely that the mean MCS scores returned to normal over time and we have added this comment to the discussion (Page 7, Line 7).

b) Similarly, we were reluctant to exclude the data from Patient #3 post hoc as this patient was the only patient to require ICU admission and exclusion of their follow-up data could bias the results towards overestimating improvement. However, their score was omitted as per the Reviewer’s suggestion when we calculated the change scores (see below).

c) We have added a column of change in PCS and MCS scores to Table 2. The mean PCS and MCS change scores are also presented in the text. A sensitivity analysis calculating the mean PCS and MCS without Patient #6 was also presented in the text.

d) We were reluctant to only include mean change scores for time points with all data as we wanted to use as much of the data as possible; by excluding certain time points we would be losing important data.

Reviewer 2
This study reports long term outcome (mean of 1.1 years) of 7 patients with acute flaccid paralysis following West Nile Virus infection. Outcome measurement was achieved using a 36 item short-form (SF-36) with questionnaire relating to physical and mental health. The important contribution of this study to the literature is the measurement of the impact of the impaired physical function on quality of life in cases of acute flaccid paralysis using a validated scale. Carson, PJ, Konweko P, Wold KS, et al reported neurocognitive impairment in patients without overt encephalitis (Carson PJ, Konweko P, Wold KS, et al. Long-term clinical and neuropsychological outcomes of West Nile virus infection. Clin Infect Dis 2006; 43:723-30). In this present study the authors noted elevated cerebrospinal fluid pleocytosis and elevated protein levels in their 7 patients. West Nile virus specific IGM antibody in CSF was performed or not is not known as it was not reported. Based on CSF findings, it is quite conceivable that these patients with flaccid paralysis had concomitant presence of encephalitis. However, this did not appear to be severe as evidenced by the improvement and normalization of the MCS scores. Sejvar JJ, Bode AV, Marfin AA, et al. (West Nile virus-associated flaccid paralysis outcome. Emerg Infect Dist 2006; 12:514-16) and Cao NU. Ranganathan C, Kupsky WJ, Li J (Recovery and prognosticators of paralysis in West Nile virus infection. J Neurol Sci 2005; 236:73-80) in their studies had reported that most strength recovery to occur during first 6-8 months following weakness onset. The mean follow up time of these 7 patients case series of 1.1 years should be more than adequate to capture physical function. Overall, this was a good case report.
We thank this reviewer for their thoughtful comments. We agree that concomitant presence of non-severe encephalitis could not be ruled out and have added this limitation to the discussion (Page 7, Line 9).

**Editorial Request**

Please include a Consent section at the end of the manuscript, before the reference list. This should contain a statement to confirm that informed written consent was received for publication of the manuscript and figures. We recommend the following wording: Written informed consent was obtained from the patient(s) for publication of this manuscript and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal." It is a requirement to have written informed consent from the patient for publication of the case and we will not proceed with your manuscript until you have confirmed this.

This comment has been added at the end of the manuscript on Page 8, Line 2.

Respectfully submitted on behalf of the authors,

Jennie Johnstone

Jennie Johnstone, MD
Assistant Professor,
Division of Infectious Diseases,
Department of Medicine,
McMaster University