



Letter to the Editor

Cardiovascular comorbidities in patients with West Nile disease infection: An unexplored issue



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To the Editor,

Over the latest years, the incidence of West-Nile virus (WNV) infection has increased dramatically in some Italian regions, as in the North-east of Italy [1,2]. However, data regarding the prevalence of cardiovascular (CV) comorbidities and their potential impact on the short-term outcome of these patients have never been investigated. Generally, preexisting chronic conditions such as CV (CVD), metabolic and respiratory diseases are often associated with a greater risk of progression to a worst outcome. Aim of the present study is to assess the prevalence of CV comorbidities and their potential effect on the short-term survival in patients with confirmed WNV infection.

We retrospectively reviewed the clinical records of consecutive patients with confirmed WNV infection evaluated in our Institution between the 1st June and the 1st October 2018. Specifically, West Nile infection was always confirmed with serum and/or cerebrospinal fluid markers. Patients having an history of arterial hypertension (HT), previous myocardial infarction, transient ischemic attack (TIA), stroke, cardiomyopathies, valvular heart disease, carotid artery disease, arrhythmias or venous thromboembolism (VTE) were labeled as having CVDs. As cardiovascular comorbidities we considered obesity, diabetes mellitus (DM) and dyslipidemia. HT was defined according the European society of Hypertension guidelines [3]. Body mass index was calculated (in kg/m^2) as the ratio of weight to squared height; subjects were considered obese if BMI was $\geq 30 \text{ kg}/\text{m}^2$. Patients were labeled as diabetic if repeatedly fasting glucose was $\geq 126 \text{ mg}/\text{dl}$ or when having a confirmed history, by previous medical records, of DM or when in treatment with antidiabetic drugs. In all cases, comorbidities were always confirmed by hospital or physician records. The entire cohort has been stratified according to the presence or absence of previous history of cardiovascular disease (CVDs) and considering the involvement of the central nervous system [West Nile neuroinvasive (WNND) and non-neuroinvasive (WNN-ND) forms, respectively]. A six-month follow-up was performed. Mortality during in-hospital stay was obtained from an electronic clinical database for patients maintained at our institution and by review of hospital records for those discharged to referring hospitals. Conversely, post-discharge survival status was obtained from the Municipal Civil Registries. The study was approved by the local

boards and all procedures were in accordance with the Declaration of Helsinki and with institutional guidelines. Continuous variables were expressed as mean \pm standard deviation (SD) and were compared by Student's *t*-test if the data had normal distribution, otherwise by Wilcoxon-Mann-Whitney *U* test. Categorical variables were presented as proportions and compared by the Pearson's χ^2 test. Multiple stepwise logistic regression analysis was used to assess independent predictors of encephalitis and of prolonged hospital stay (≥ 7 days). Logistic coefficients were used for estimating the odds ratios (OR) with 95% confidence intervals (CI); Hosmer-Lemeshow (H-L) test was also performed. To estimate six-month survival, the Kaplan–Meier method was applied, and the log-rank test was used to evaluate the differences between patients with and without CVDs. Statistical significance was defined as $p < .05$. Statistical analyses were performed using SPSS package version 20.0 (SPSS, Chicago, IL, USA).

Over the study period, 52 consecutive patients were retrospectively identified (28 males and 24 females, mean age 59.4 ± 16.7 years old). Sixteen patients (30.7%) had a WNND. Patients with and without an history of CVDs were 19 (36.5%) and 33 (63.4%), respectively. As expected, subjects with CVDs were older (66.3 ± 13.2 vs 55.4 ± 17.4 years, $p = .02$) and more frequently with a past medical history of neurological disease (31.6% vs 3.0%, $p = .005$). No significant differences were observed regarding the initial signs and symptoms of the infection. Indeed, the frequency of headache, fever, dysarthria, myalgia, morbilliform or maculopapular rash, weakness and gastrointestinal symptoms were comparable between patients with and without CVDs. Conversely, patients with CVD, at admission, showed a higher systolic (SBP) and diastolic blood pressure (DPB) (136.3 ± 9.4 vs 121.6 ± 3.0 , $p = .01$ and $76.5 \pm 7.3 \text{ mmHg}$ vs $69.6 \pm 14.0 \text{ mmHg}$, $p = .02$, respectively). No significant differences were observed comparing the abnormalities detected in complete blood counts at admission, as anemia, leukocytosis, leukopenia and/or thrombocytopenia among the two groups. As predictable, patients with CVD more frequently had an history of DM (15.8% vs 0%, $p = .002$) and obesity (26.3% vs 3.0%, $p = .003$). Moreover, patients with previous history of CVDs more often required hospitalization (73.6% vs 36.3%, $p = .01$) for a longer period (10.2 ± 12.7 vs 4.0 ± 8.0 days, $p = .03$) when compared to those patients without CVDs. Over a six months follow-up,

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the mortality rate was 9.6% ($n = 5$) all due to a WNND. Among these, 2 patients (40%) had a previous history of CVDs. However, due the limited numbers of events and patients enrolled, the Log-rank (Mantel Cox) analysis performed to assess a potential difference in the six-month survival among patients with and without CVDs not reached the statistical significance ($p = .87$).

Patients with WNND who developed an encephalitis ($n = 19$) more frequently had a HT (31.2% vs 5.6% $p = .01$) and DM (21.0% vs 0%, $p = .003$) when compared to WNN-ND subjects. Multivariate logistic regression analysis demonstrates that history of CVDs (OR 2.4, 95% CI 2.1–3.3, $p = .0001$), was an independent predictor of prolonged hospital stay (≥ 7 days) in patients with WNV infection, independently from DM (OR 1.96, 95% CI 1.82–2.25, $p = .02$) and WNND (OR 1.88, 95% CI, $p = .003$) (H-L test chi-square 3.54, $p = .60$). Moreover, HT resulted an independent predictor of encephalitis (OR 6.21, 95% CI 5.22–7.91, $p < .001$), independently from DM (OR 3.28, 95% CI 2.96–3.98, $p = .001$) and age ≥ 65 years (OR 2.01, 95% CI 1.54–2.61, $p = .002$) (H-L test chi square 6.14, $p = .78$).

Our small study demonstrates that in patients with WNV infection, about one-third of patients have a previous history of CVDs, requiring a prolonged hospital stay when compared to those without CVDs. Moreover, HT was an independent predictor of encephalitis in WNV patients. About half of patients died during a six-month follow-up showed a history of CVDs. The relationship between WNV infection and CVDs has been poorly investigated. Indeed, only few studies have reported sporadic data regarding the cardiovascular comorbidities of patients enrolled. Badowi et al., in a large meta-analysis based on 18 studies, have collected these data demonstrating that HT (45%, 95% CI 39.1–51.0), DM (24.7%, 95% CI 20.2–29.8) and heart disease (25.6%, 95% CI 19.5–32.7) were the most prevalent comorbidities in patients with WNV infection, especially in patients with a severe disease [4]. Similarly, Patel et al., after reviewing 67 studies reported that some population groups, as elderly or patients with CVD or cancer were at greater risk of severe neurological sequelae and/or diseases after the WNV infection [5]. Despite the association between a longer in-hospital stay and patients with multiple comorbidities in predictable, the relationship between HT and encephalitis appears important. Probably, HT leads to increased permeability of the blood-brain barrier, increasing the viral dissemination into the central nervous system [6]. Moreover, HT resulted associated with WNND phenotype

independently from the presence of DM, which is responsible of an immune dysregulation [7]. Our investigation has obviously some limitations, as the relatively small number of patients enrolled, the retrospective and monocentric design of the study and the absence of systematic screening for all patients enrolled. However, our preliminary results, which must be confirmed in further larger, prospective and multicentric studies, for the first time highlights the impact of chronic CVDs in the hospital course and outcome of patients with WNV infection.

Conflict of interest

None of the authors have conflicts of interest to declare.

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