RESEARCH

Risk of stroke in patients with dengue fever: a population-based cohort study

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ABSTRACT

BACKGROUND: Stroke is a severe neurologic complication of dengue fever, described in only a few case reports. The incidence and risk factors for stroke in patients with dengue remain unclear. We conducted a population-based retrospective cohort study to investigate the risk of stroke in patients with dengue.

METHODS: Using data from the Taiwan National Health Insurance Research Database, we included a total of 13 787 patients with dengue newly diagnosed between 2000 and 2012. The control cohort consisted of patients who did not have dengue, matched 1:1 by demographic characteristics and stroke-related comorbidities. We calculated the cumulative incidences and hazard ratios (HRs) of stroke in both cohorts using Kaplan–Meier curves and Cox proportional hazards regression.

RESULTS: The overall incidence rate of stroke was 5.33 per 1000 person-years in the dengue cohort and 3.72 per 1000 person-years in the control cohort, with an adjusted HR of 1.16 (95% confidence interval [CI] 1.01–1.32). The risk of stroke among patients with dengue was highest in the first 2 months after diagnosis (25.53 per 1000 person-years, adjusted HR 2.49, 95% CI 1.48–4.18).

INTERPRETATION: Dengue fever was associated with an increased risk of stroke in the first few months after diagnosis. The effect of dengue on stroke may be acute rather than chronic.

Dengue is a globally important mosquito-borne viral infection, with about 4 billion people at risk and 100 million symptomatic cases annually.[1] In 1997, the World Health Organization (WHO) classified symptomatic dengue as dengue fever and dengue hemorrhagic fever, with the latter having 4 grades of severity, where grades III and IV were considered to represent dengue shock syndrome.[2] Dengue hemorrhagic fever is a more severe form of dengue fever, with evident plasma leakage leading to spontaneous bleeding, organ failure or hypovolemic shock. In 2009, the WHO published a new classification for dengue, adding central nervous system (CNS) involvement as a criterion for severe dengue.[3] Complications of CNS involvement in severe dengue include dengue encephalopathy or encephalitis, post-dengue immune-mediated syndromes and cerebrovascular complications.[4] The mediators released during dengue infection, such as cytokines, chemokines and complement, have vasoactive or procoagulant effects leading to thrombocytopenia, disseminated intravascular coagulation and vasculitis, which may result in stroke.[4] It is challenging to treat stroke in patients with dengue because of the difficulty of administering thrombolytic agents to patients with a bleeding tendency. Knowing the incidence of and risk factors for stroke in patients with dengue would be helpful. However, only a few cases of dengue-related hemorrhagic or ischemic stroke have been reported.[5–9] The risk of stroke in patients with dengue remains unclear.

In Taiwan, patients with dengue are under surveillance by the Centers for Disease Control, R.O.C. (Taiwan) (known as the Taiwan CDC), through a routine laboratory-based screening and diagnosis system.[10] All hospital-diagnosed cases of dengue must be reported to the Taiwan CDC for confirmation and subsequent surveillance. We conducted a population-based cohort study using data from the Taiwan National Health Insurance Research Database (NHIRD), to investigate the risk of stroke in patients with dengue, and compared this risk with the risk in a matched population of patients without dengue. We also performed subgroup analyses to examine the risk differences.

Methods

Data source

For this retrospective cohort study, we retrieved data concerning patients with dengue from the NHIRD, which enrolled about 26 million residents in Taiwan between 1996 and 2013, covering more than 99% of the population of Taiwan. The database contained detailed health care information for each enrollee, with encryption to protect personal privacy. Disease identification in the NHIRD follows the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). Previous studies have validated the accuracy of disease diagnosis in the NHIRD,

including diagnosis of ischemic stroke, showing high sensitivity (94.5%–97.3%) and high positive predictive value (88.4%–97.8%).[11,12] The Bureau of National Health Insurance in Taiwan routinely reviews medical charts and claims to ensure the validity and accuracy of data coding in the NHIRD.

Study population and outcome

The study population comprised 2 cohorts: the dengue and control cohorts. The dengue cohort consisted of all cases of dengue newly diagnosed in hospital between 2000 and 2012, specifically dengue fever (ICD-9-CM code 061) and dengue hemorrhagic fever (ICD-9-CM code 065.4). To avoid surveillance bias related to hospital admission, the control cohort consisted of hospital inpatients without a diagnosis of dengue. For each patient, the index date was defined as the date of first diagnosis of dengue fever or dengue hemorrhagic fever (dengue cohort) or the admission date (control cohort). We defined patients with separate diagnosis dates during the follow-up period as having repeat dengue infections.

The main study outcome was stroke (ICD-9-CM codes 430–437), as documented in hospital records. We also assessed hemorrhagic stroke (ICD-9-CM codes 430–432) and ischemic stroke (ICD-9-CM codes 433–434) in our stratified analysis. We excluded patients with stroke or late effects of stroke (ICD-9-CM codes 430–438) occurring before the index date and those with missing information during follow-up. To control confounding related to other recent infections,[13,14] we also excluded patients with any bacterial, viral or other infection within 2 months before the index date.

We followed all participants from the index date to the first of date of outcome, date of death or end of 2013. We used a propensity-score matching method to match each patient with dengue with 1 control patient on the following characteristics: sex, age, year of index date and covariables listed in Table 1.

The diagnosis of dengue was confirmed by laboratory testing, according to any of the criteria of the Taiwan CDC: positive result on testing for dengue virus genome by real-time polymerase chain reaction; detection of dengue virus nonstructural protein 1 (NS1); positive seroconversion or a fourfold or greater increase in dengue-specific immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies from acute and convalescent paired serum samples; high-titre dengue-specific IgM/IgG antibody in acute serum samples; or isolation of dengue virus.[10] The case definition for dengue hemorrhagic fever was proven dengue according to criteria of the WHO: signs of hemorrhagic tendency, thrombocytopenia (≤ 100 × 10^9/L) and evidence of plasma leakage (≥ 20% increase in hematocrit, clinical fluid accumulation or hypoproteinemia).[2]

Assessment of covariables

We adjusted the statistical model for comorbidities associated with stroke, including atrial fibrillation or flutter, cancer, chronic obstructive pulmonary disease (COPD), chronic renal failure, diabetes mellitus, dyslipidemia, heart failure, hypertension and ischemic heart disease.[15,16] As a measure of the severity of stroke and underlying diseases, we assessed the total admission days for each participant.[17,18] Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170994/-/DC1) lists the detailed ICD-9-CM codes for covariables in this study. We also used hospitalization records to identify comorbidities, using validated algorithms.[19]

Statistical analysis

We tested the differences in baseline characteristics between the 2 cohorts by χ^2 and 2-sample Student *t* tests. We used a

Table 1: Baseline characteristics in control and dengue cohorts

Variable	Group; no. (%) of participants* Control *n* = 13 787	With dengue *n* = 13 787	*p* value*
Sex			0.005
Female	6628 (48.1)	6862 (49.8)	
Male	7159 (51.9)	6925 (50.2)	
Age, yr, mean ± SD	44.2 ± 14.3	44.6 ± 19.3	0.05
≤ 30	2336 (16.9)	3581 (26.0)	
31–60	9528 (69.1)	6886 (49.9)	
> 60	1923 (13.9)	3320 (24.1)	
Total admission days, mean ± SD	10.8 ± 97.6	10.5 ± 51.5	0.7
Comorbidity			
Atrial fibrillation and flutter	62 (0.4)	64 (0.5)	0.9
Cancer	330 (2.4)	292 (2.1)	0.1
COPD	390 (2.8)	371 (2.7)	0.5
Chronic renal failure	79 (0.6)	86 (0.6)	0.6
Diabetes mellitus	645 (4.7)	625 (4.5)	0.6
Dyslipidemia	347 (2.5)	306 (2.2)	0.1
Heart failure	139 (1.0)	133 (1.0)	0.7
Hypertension	898 (6.5)	876 (6.4)	0.6
Ischemic heart disease	440 (3.2)	447 (3.2)	0.8
Follow-up, yr, mean ± SD	7.89 ± 3.71	7.58 ± 3.77	NA
Top 5 reasons for admission†			NA
Digestive	8865 (64.3)	DF: 12 477 (90.5)	
Cardiopulmonary	783 (5.7)	DHF: 1310 (9.5)	
Metabolic	533 (3.8)		
Trauma	398 (2.9)		
Genitourinary	226 (1.6)		

Note: COPD = chronic obstructive pulmonary disease, DF = dengue fever, DHF = dengue hemorrhagic fever, NA = not applicable, SD = standard deviation.
*Student *t* test for continuous variables and χ^2 test for categorical variables.
†For patients in the dengue group , there were only 2 top reasons: dengue fever and dengue hemorrhagic fever.

multivariable Cox proportional hazard model, with adjustment for sex, age, covariables and the competing risk of death, to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke. We performed stratified subgroup analyses with both single-variable and multivariable Cox proportional hazard models. We also conducted sensitivity analyses with alternative controls matched by propensity score. We used the Kaplan–Meier method to compare the cumulative incidences of stroke between the 2 cohorts with the log-rank test. We verified the assumption of proportional hazards with the graphical plotting method. We tested the seasonality of stroke in this study with the χ^2 goodness-of-fit test.

We performed all statistical analyses with SAS statistical software, version 9.4 (SAS Institute), with significance set at $\alpha = 0.05$.

Ethics approval

The study was approved by the Institutional Review Board of the China Medical University Hospital (CMUH104-REC2–115-CR2), which waived the requirement for informed consent because data in the NHIRD are de-identified.

Results

After matching, 13 787 patients were included in each of the dengue and control cohorts (Figure 1). The 2 cohorts had nearly equal proportions of females and males (Table 1), although the slightly greater proportion of males in the control cohort was statistically significant. No other baseline characteristics were significantly different. Most patients were between 31 and 60 years of age. The mean follow-up period was 7.58 and 7.89 years in the dengue and control groups, respectively. The top 5 reasons for admission for the control group were digestive disorders (e.g., peptic ulcer, diarrhea, hemorrhoids), cardiopulmonary disorders (e.g., hypertension, arrhythmia, ischemic heart), metabolic disorders (e.g., diabetes, dyslipidemia), trauma and genitourinary disorders (e.g., urolithiasis, chronic renal failure).

The overall incidence rate of stroke was higher in the dengue cohort than in the control cohort (5.33 v. 3.72 per 1000 person-years), with adjusted HR of 1.16 (95% CI 1.01–1.32) (Table 2). Females in the dengue cohort and patients without comorbidities in the dengue cohort had higher risk ratios for stroke than those in the control cohort (for females, adjusted HR 1.32, 95% CI

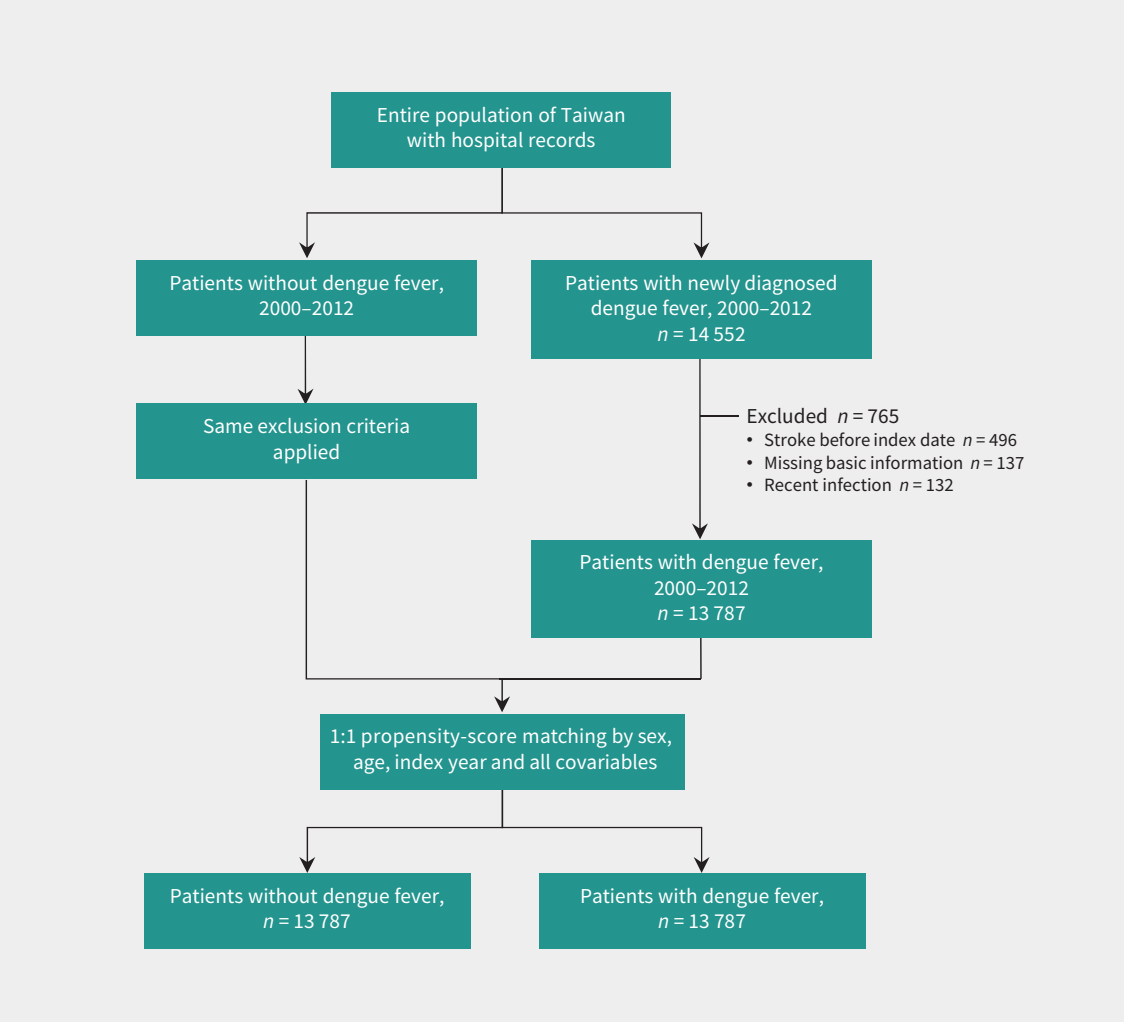

Figure 1: Flowchart for patient selection.

1.07–1.62; for those with no comorbidities, adjusted HR 1.31, 95% CI 1.10–1.56). The proportion of patients with stroke who were admitted to the intensive care unit did not differ significantly between the dengue and control cohorts (28/557 [5.0%] v. 24/405 [5.9%], $p = 0.5$).

Time trends for risk of stroke

The incidence rate of stroke in the dengue cohort showed a time-dependent trend during the follow-up period (Table 3). The risk of stroke in the dengue cohort, relative to the control cohort, was highest in the first 2 months (25.53 per 1000 person-years; adjusted HR 2.49, 95% CI 1.48–4.18) and then declined as the follow-up period increased. The risk of hemorrhagic and ischemic strokes showed a similar trend: highest in the first 2 months (for hemorrhagic stroke, adjusted HR 8.72, 95% CI 1.10–68.9; for ischemic stroke, adjusted HR 2.90, 95% CI 1.35–6.26). The difference in cumulative incidence of stroke between the 2 cohorts appeared early in the follow-up period (Appendix 2, Part 1, available at

Table 2: Comparison of incidence and hazard ratio of stroke between dengue and control cohorts

	Control cohort			Dengue cohort				
Variable	No. of events	PY	Rate*	No. of events	PY	Rate*	Crude HR (95% CI)	Adjusted HR† (95% CI)
Total stroke	405	108 847	3.72	557	104 563	5.33	1.43 (1.26–1.63)	1.16 (1.01–1.32)
Sex								
Female	145	53 320	2.72	251	53 298	4.71	1.72 (1.40–2.11)	1.32 (1.07–1.62)
Male	260	55 527	4.68	306	51 265	5.97	1.28 (1.08–1.51)	1.06 (0.89–1.25)
Stratified by age, yr								
≤ 30	7	19 885	0.35	9	28 177	0.32	0.87 (0.32–2.33)	0.84 (0.31–2.27)
31–60	183	76 709	2.39	193	54 186	3.56	1.51 (1.23–1.85)	1.48 (1.21–1.82)
> 60	215	12 252	17.55	355	22 200	15.99	0.90 (0.76–1.07)	0.99 (0.83–1.17)
Comorbidity								
No	215	98 654	2.18	360	93 640	3.84	1.79 (1.51–2.12)	1.31 (1.10–1.56)
Yes	190	10 193	18.64	197	10 924	18.03	0.96 (0.78–1.17)	0.91 (0.75–1.12)

Note: CI = confidence interval, HR = hazard ratio, PY = person-years.
*Incidence rate, per 1000 person-years.
†Adjusted for sex, age, total days of admission and comorbidity in Cox proportional hazards regression.

Table 3: Risk trends for stroke in each cohort, stratified by follow-up period and type of stroke

	Control cohort			Dengue cohort				
Type of stroke and follow-up period, mo	No. of events	PY	Rate*	No. of events	PY	Rate*	Crude HR (95% CI)	Adjusted HR† (95% CI)
Any stroke								
≤ 2	19	2292	8.29	58	2272	25.53	3.06 (1.82–5.13)	2.49 (1.48–4.18)
3–12	42	11 351	3.7	57	11 250	5.07	1.37 (0.92–2.04)	1.18 (0.79–1.75)
> 12	344	95 204	3.61	442	91 041	4.85	1.34 (1.17–1.55)	1.13 (0.98–1.30)
Hemorrhagic stroke								
≤ 2	1	2293	0.44	10	2279	4.39	10.01 (1.28–78.17)	8.72 (1.10–68.9)
3–12	8	11 376	0.7	14	11 303	1.24	1.76 (0.74–4.20)	1.57 (0.67–3.69)
> 12	58	96 593	0.6	74	92 931	0.80	1.31 (0.93–1.85)	1.17 (0.83–1.65)
Ischemic stroke								
≤ 2	8	2293	3.49	29	2276	12.74	3.63 (1.66–7.94)	2.90 (1.35–6.26)
3–12	20	11 367	1.76	26	11 282	2.3	1.31 (0.73–2.34)	1.09 (0.61–1.94)
> 12	180	96 011	1.87	258	91 954	2.81	1.51 (1.24–1.82)	1.21 (1.00–1.47)

Note: CI = confidence interval, HR = hazard ratio, PY = person-years.
*Incidence rate, per 1000 person-years.
†Adjusted for sex, age, total admission days and comorbidity in Cox proportional hazards regression.

www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170994/-/DC1) and was statistically significant ($p < 0.001$). The result of seasonality testing showed no significant seasonal effect ($p = 0.5$).

Risk factors for stroke

Appendix 2, Part 2 shows that patients with dengue hemorrhagic fever had the highest incidence rate of stroke (7.92 per 1000 person-years), with an adjusted HR of 1.40 (95% CI 1.10–1.77), followed by patients with repeat dengue infection (6.85 per 1000 person-years; adjusted HR 1.19, 95% CI 0.80–1.77) and patients with dengue fever (4.96 per 1000 person-years; adjusted HR 1.14, 95% CI 1.00–1.31).

In the multivariable analysis of risk factors for stroke (Appendix 2, Part 3), dengue was an independent risk factor for stroke (adjusted HR 1.18, 95% CI 1.03–1.34). Diabetes was the highest risk factor for stroke (adjusted HR 2.01, 95% CI 1.66–2.43), followed by dyslipidemia (adjusted HR 1.49, 95% CI 1.15–1.92), male sex (adjusted HR 1.46, 95% CI 1.29–1.67), hypertension (adjusted HR 1.45, 95% CI 1.20–1.76) and age (adjusted HR 1.07 per year, 95% CI 1.06–1.07). The sensitivity analyses with alternative controls matched by propensity score had results similar to those of the main analyses (Appendix 2, Parts 4 and 5).

Interpretation

This study showed that patients with dengue had an increased risk of stroke, and this risk was time-dependent, as high as 2.49 times relative to control patients in the first 2 months. Patients with dengue who were male, who were older than 60 years or who had comorbidities had a higher incidence of stroke. The increased risk ratio for stroke in patients with dengue was greater for females and for those without comorbidity. It may be that male sex and comorbidities (including diabetes, dyslipidemia and hypertension) are stronger risk factors for stroke than dengue, and thus may mask the effects of dengue.

We found that patients with dengue had a higher risk of both hemorrhagic and ischemic stroke. Compared with previous studies reporting more hemorrhagic strokes than ischemic strokes among patients with dengue,[5–9] we observed more ischemic strokes. This difference may be related to universal screening for and surveillance of dengue, and to high medical accessibility in Taiwan, which could improve the early detection of ischemic stroke among patients with dengue. It is uncertain whether reported dengue-related hemorrhagic strokes were due to direct hemorrhage or to hemorrhagic conversion from ischemic stroke. Carod-Artal and associates[4] also assumed that dengue-related ischemic strokes might be underestimated. In our study, patients with dengue hemorrhagic fever had a higher risk of stroke than patients with dengue fever, which indicates that the pathogenesis of dengue hemorrhagic fever may play a role in the occurrence of stroke.

The mechanisms of dengue-related stroke are under investigation. Multiple pathways have been proposed, with the major focus on endothelial dysfunction leading to plasma leakage.[20,21] Dengue virus could infect immune cells, inducing complex cascades of inflammatory mediators, such as cytokines, chemokines and complement. The interaction of these mediators with endothelial cells increases endothelial permeability and reduces the integrity of the endothelial barrier.[20] Moreover, cross-reaction of anti-NS1 antibodies and direct viral infection of endothelial cells and platelets contribute to hemorrhage, thrombocytopenia and plasma leakage.[22,23] These immune-mediated mechanisms of dengue hemorrhagic fever in peripheral blood have also been found in the brain, where they cause breakdown of the blood–brain barrier, leukocyte infiltration and local inflammation, followed by vasoconstriction, thromboembolism, cerebral edema, ischemia and hemorrhage.[4,21,24] A few case reports have shown atrial fibrillation as a complication of severe dengue, which may predispose these patients to stroke.[25,26]

The time trends for dengue-related stroke in this study suggest that the effects of dengue on stroke may be acute rather than chronic. Previous studies found that the inflammatory mediators and antigen–antibody complex caused by dengue were transient.[20,21] Furthermore, reported cases of dengue-related stroke have ranged from 2 to 22 days after onset of fever.[5–9]

Limitations

This study had some limitations. In Taiwan, cases of dengue are clustered seasonally.[27] However, we found no significant seasonality leading to bias for the stroke cases in our study. This finding corresponds to that of a prior study indicating that there is no seasonality to ischemic stroke in Taiwan.[28] To ensure sufficient sample size and case ascertainment for patients with dengue, we used hospital records for the whole population of Taiwan; however, these records lack details about disease severity and medications. Therefore, we adjusted the data for total admission days, a measure that is highly correlated with disease severity.[17,18] Total admission days and the proportion of patients admitted to the intensive care unit were comparable between the 2 study groups. To address potential confounding related to medications, we performed a subgroup analysis of patients without comorbidities, who would be less likely to receive medications such as antithrombotic or antihypertensive agents for stroke prevention; the results were consistent with the main analysis, with a stronger effect. Thus, disease severity and medications are unlikely to have biased our conclusions. Information about smoking, diet, body mass index, daily activity and ethnicity is not recorded in the NHIRD, so we could not adjust for these confounding variables. We used COPD as a surrogate in covariable adjustment. The NHIRD does not record laboratory data, so we were unable to perform further analysis on the effects of different dengue serotypes or the patients' bleeding profiles or inflammatory markers. Given the inherent limitations of administrative data, systematic bias, such as coding errors, was inevitable.

Conclusion

In this population-based study, the presence of dengue was associated with an increased risk of stroke. The effect of dengue on stroke may be acute rather than chronic. Clinicians in dengue-endemic areas should be aware of this association, especially for patients with dengue who have neurologic deficits or for patients with stroke who have unexplained fever. Our findings may help with clinical risk evaluation and may serve as a basis for further investigation of the pathogenesis of dengue-related stroke.

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