Diabetes and the Severity of Pandemic Influenza A (H1N1) Infection

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OBJECTIVE — To confirm the existence of an increased risk of complications from influenza A (H1N1)p among patients with diabetes.

RESEARCH DESIGN AND METHODS — Using data from an enhanced influenza surveillance project in Montreal, Canada, and age/sex-specific population estimates of diabetes prevalence, we estimated the risk of hospitalization among persons with diabetes. Comparing hospitalized patients admitted or not to an intensive care unit (ICU), we estimated the risk of ICU admission associated with diabetes, controlling for other patient characteristics.

RESULTS — Among 239 hospitalized patients with PCR-confirmed influenza A (H1N1)p, 162 (68%) were interviewed, of whom 22 had diabetes, when 7.1 were expected (prevalence ratio 3.10 [95% CI 2.04–4.71]). The odds ratio for ICU admission was 4.29 (95% CI 1.29–14.3) among hospitalized patients with diabetes compared to those without.

CONCLUSIONS — Diabetes triples the risk of hospitalization after influenza A (H1N1)p and quadruples the risk of ICU admission once hospitalized.

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D iabetes increases the likelihood of medical consultation (1) and risk of death (2) due to influenza. Conversely, the risk of respiratory illness and of hospitalization within 14 days of a diagnosis of influenza in patients with diabetes may be reduced by oseltamivir (3). Also, diabetic patients are targeted for immunization against seasonal (4) and pandemic (p) influenza A (H1N1) (5). Three recently published case series (6–8) of patients with influenza A (H1N1)p may be interpreted (7) as corroborating for pandemic influenza the known association of diabetes with complications of seasonal influenza, but do not quantify the increase in risk. We report population-based estimates of risk ratios for severe influenza A(H1N1)p in the presence and absence of diabetes.

RESEARCH DESIGN AND METHODS — As part of an enhanced surveillance project, the 239 residents of

Montreal with a PCR-positive specimen for influenza A (H1N1)p collected between 25 May and 1 July 2009 and hospitalized in connection with the infection were targeted for telephone interviews. The questionnaires could be answered by the patient or a proxy, but no medical records were reviewed. Diabetes prevalence in Montreal for 2005 by sex and age-group (age <20, 20–44, 45–64 and 65+ years), estimated from health care utilization data (9) and complemented for the <20 age-group by Canadian information (10), was used to estimate the expected number of persons with diabetes among our subjects. The number of subjects in each sex/age-group was multiplied by the diabetes prevalence rate in this group, and the results were summed over all sex/age-groups to obtain the overall expected number of subjects with diabetes. Also, questionnaire responses were compared between subjects admitted to an intensive care unit (ICU), i.e., the case

subjects, and those hospitalized without ICU admission, i.e., the control subjects. The associations between patient characteristics and ICU admission and/or diabetes were first assessed by univariate methods. Characteristics associated with both ICU and diabetes at the $P < 0.05$ level were entered into a multivariate logistic regression model of the effect of diabetes on ICU admission, to control for the effect on the risk of ICU admission of differences between subjects with and without diabetes other than the disease itself (confounding).

RESULTS — The participation rate was 68%, for a total of 162 subjects. Nonparticipation was mostly due to the patients and their proxies being unreachable (58 of 77); refusals were rare (6 of 77).

The average age of subjects was 28.6 years, and their median age was 21 years (range <1–85); 45.1% were male. There were seven deaths, including three among diabetic subjects. A history of diabetes was reported for 13.6% (22 of 162), 5.6% (9 of 162) for type 1 diabetes, and 8.0% (13 of 162) for type 2 diabetes. Based on population rates, a total of 7.10 diabetic subjects would have been expected, yielding a prevalence ratio of 3.10 (22/ 7.1) with a 95% CI from 2.04 to 4.71 (11).

ICU admission was required for 19.1% (31 of 162) of patients. Of these, 32.3% (10 of 31) were diabetic, whereas among the non-ICU patients the diabetic proportion was 9.2% (12 of 131) (Fisher exact test, $P = 0.002$). Only two patient characteristics, age and chronic cardiac disease, were associated with both diabetes and ICU admission. Not associated with ICU admission were sex, pregnancy at time of infection, a history of asthma or chronic obstructive pulmonary disease, a history of any other chronic disease, level of schooling, occupational category, country of birth (Canada vs. other), smoking, BMI, immunosuppression, previous immunization against seasonal influenza, antiviral treatment, and delay between symptom onset and hospitalization.

Table 1 shows the associations between ICU admission and combinations of risk factors. The odds ratio (OR) for diabetes in model 4 shows that, by itself,

Table 1—*Characteristics of hospitalized patients admitted to an ICU compared to those who were not*

	Model 1*	Model 2†	Model 3	Model 4
Diabetes				
No	1	1	1	1
Yes	4.29 (1.29–14.3)	4.36 (1.38–13.8)	4.61 (1.58–13.4)	4.72 (1.81–12.3)
Age (years)				
0–19	1	1		
20–49	3.17 (1.16–8.69)	3.25 (1.20–8.86)	—	—
50+	1.36 (0.39–4.81)	1.49 (0.44–5.07)		
Cardiac disease				
No	1		1	
Yes	1.77 (0.61–5.16)	—	1.67 (0.61–4.62)	—

Data are aOR (95% CI). aOR estimated by logistic regression. *Models 1 and 3 include 160 subjects, because of missing information on chronic cardiac disease for 2 subjects. †Models 2 and 4 include all 162 subjects. —, corresponding factor is not in the model. In the multivariate models, the aOR are adjusted for all the other terms in the model.

diabetes increased the risk of ICU admission 4.72 times, and the adjusted odds ratio (aOR) of 4.29 in model 1 shows that the increase is largely independent of differences in age and chronic cardiac disease between patients with and without diabetes. Type of diabetes had no effect on the OR: type 1 diabetes OR 4.53 (95% CI 1.12–18.3), type 2 diabetes OR 4.86 (95% CI 1.49–15.9). Controlling for age (associated with type) did not substantially alter these ORs.

CONCLUSIONS — Among our hospitalized influenza A (H1N1)p patients, 14% reported having diabetes, which is similar to recently reported proportions: in Mexico, 17% of 58 critically ill patients had the disease (6), as did 21% of 168 in Canada (7), and 11% of 1,088 hospitalized or deceased patients in California (8). Our results corroborated the impression that persons with diabetes who contract influenza A (H1N1)p are more likely than others to be hospitalized or to require ICU care. As previously reported for infection-related mortality in diabetic patients (12), ICU risk was independent of the presence of coexisting heart disease. For patient characteristics not associated with the outcome, the small sample size precludes conclusions about a true absence of association.

We have no information on whether Montrealers with diabetes were more likely than others to be tested for (H1N1)p infection, which could have resulted in overrepresentation in our study. However, by design all our subjects were hospitalized; 66% (100 of 151) were tested for (H1N1)p on the day of admission, and only 24% (5 of 21) of those with

diabetes and 25% (33 of 130) of those without had been tested earlier, suggesting that the reason for testing was current health status, not diabetes. Participation is also unlikely to have been affected by diabetes status, because the questionnaire had only two questions on diabetes.

Aboriginal status of our subjects was unknown; however, given the low proportion of aboriginals in Montreal (0.45%; J. Massie, Montreal Health and Social Services Agency, Montreal, Canada; personal communication) and the small number of subjects with diabetes in this study, its power to detect confounding of the effect of diabetes by that of aboriginal status would have been minimal.

Estimates of the risk of influenza A (H1N1)p infection in persons with diabetes would complement estimates of the risk of hospitalization and of ICU care after infection. Risk estimates for seasonal influenza could strengthen the basis for recommendations that persons with diabetes be regularly immunized against influenza.

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