Increased Risk of Rehospitalization for Acute Diabetes Complications and Suicide Attempts in Patients With Type 1 Diabetes and Comorbid Schizophrenia

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OBJECTIVE

The aim of this large retrospective cohort study was to estimate the supplementary morbidity and mortality risks conferred by the co-occurrence of schizophrenia among young people with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This nationwide population-based study included individuals aged 15–35 years hospitalized in France for type 1 diabetes from 2009 to 2012 with or without schizophrenia. For assessment of the occurrence of rehospitalization for acute diabetes complications, suicide attempts, and hospital mortality, multivariate logistic regressions and survival analysis adjusted for age, sex, and Charlson Comorbidity Index scores were performed. The association between hospitalization for suicide attempts and acute diabetes complications was further explored in a survival analysis, with the exposure of acute diabetes complications as a time-dependent covariate.

RESULTS

Among 45,655 individuals aged 15–35 years who were hospitalized for type 1 diabetes, 341 (0.75%) had a previous or contemporary hospitalization for schizophrenia. Within 3 years of follow-up, schizophrenia was associated with increased risks of rehospitalization for hypoglycemia (adjusted odds ratio 3.21 [95% CI 1.99–5.20]), hyperglycemia (7.01 [3.53–13.90]), ketoacidosis (2.01 [1.49–2.70]), and coma (3.17 [1.90–5.27]); hospitalization for suicide attempts (12.15 [8.49–17.38]); and hospital mortality (2.83 [1.50–5.36]). Hospitalization for a suicide attempt was associated with an increased risk of hospitalization for acute diabetes complications independently from schizophrenia (hazard ratio 3.46 [95% CI 2.74–4.38]).

CONCLUSIONS

Patients suffering from the combination of type 1 diabetes and schizophrenia are at increased risk of hospitalization for acute diabetes complications as well as suicide and hospital mortality. These individuals may require specific care programs and close monitoring of mental, somatic, and social health.

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Schizophrenia is a serious chronic condition affecting 0.5–1% of the general population (1). It is associated with a 20-year reduction in life expectancy related to both suicide and physical problems (2). A number of studies have reported an increased risk of type 2 diabetes in people suffering from schizophrenia since illness onset and even in antipsychotic-naïve patients (3–5). Moreover, these patients show increased risks of hospitalization for hypo- or hyperglycemia and infections (6), suggesting poor glycemic control in these patients.

While the association between type 2 diabetes and schizophrenia is clear, the association between type 1 diabetes and schizophrenia remains controversial (7). Prevalence of schizophrenia among individuals with type 1 diabetes has been estimated between 0.20 and 1.5% (7–11). However, regarding the high risk of morbidity and mortality yielded by each of these conditions, comorbid type 1 diabetes and schizophrenia may be a problematic combination. To shed light on this association, we analyzed a large nationwide cohort of individuals younger than 35 years old and hospitalized with type 1 diabetes and explored the risk of hospitalization for complications in those with versus without schizophrenia. We hypothesized that hospitalized individuals with comorbid type 1 diabetes and schizophrenia present more rehospitalization for acute diabetes complications or for suicide attempts and a higher risk of mortality at 1- and 3-year follow-up than people with diabetes without schizophrenia.

RESEARCH DESIGN AND METHODS

We conducted a nationwide population-based retrospective cohort study of individuals aged 15–35 years hospitalized in France for type 1 diabetes from 2009 to 2012. To this aim, we used a French national database named Programme de Médicalisation des Systèmes d'Information (PMSI). This database relies on a standardized procedure that routinely collects discharge abstracts for people hospitalized in all public and private hospitals in France, including full- or part-time hospitalizations. Information includes main and associated diagnoses (secondary events and comorbidities) coded according to the World Health Organization ICD-10 and procedures performed during hospital stays using the common classification of medical procedures. For ensuring the quality of hospital data, various control procedures have previously been conducted. The very good quality of this database has been shown and has enabled us to carry out epidemiological studies based on these data (12–15).

People hospitalized with type 1 diabetes were identified through the ICD-10 codes E10 and E12–E14 as the main, related, or associated diagnoses in discharge abstracts (PMSI). To further reduce the risk of including people with inadequate diagnosis, notably, type 2 diabetes, we only recruited individuals aged $<$35 years. In France, the REDSIAM (Réseau données Sniiram) network, devoted to the development and the validation of algorithms for identifying specific diseases, has been set up for promoting the collaboration of teams working on the French national information system. The decision to use age in addition to ICD-10 codes to select patients with type 1 diabetes also seems coherent with the conclusions of the working group devoted to diabetes. Catherine Quantin also published a report for the French health insurance confirming this recommendation (16).

The first hospitalization within this period was considered as the index hospitalization. Among this sample, we identified individuals with schizophrenia on the basis of the ICD-10 codes F2 as the main, related, or associated diagnoses in at least one previous hospitalization within the 2 years preceding or including the index hospitalization. The control group included people who were never hospitalized for schizophrenia over the 2 years preceding or including the index hospitalization until 2015 (therefore including the follow-up period). As the diagnosis of schizophrenia is rare and difficult before age 15 years (17), we only recruited individuals $>$15 years old. An epidemiologic follow-up investigation was then conducted at 1 and 3 years after the index hospitalization.

Outcomes

The main outcomes of interest were *1*) hospitalization for severe acute diabetes complications identified from codes in the PMSI database, including a main diagnosis of hypoglycemia (code E16) or hyperglycemia (R730 or R739), a main or associated diagnosis of coma (E100, E110, E120, E130, or E140), or ketoacidosis (E101, E111, E121, E131, or E141); *2*) the occurrence of a suicide attempt (X60–X75); and *3*) hospital mortality during hospitalization (living status upon discharge from hospital). In this study, we selected severe acute diabetes complications that require inpatient care.

Confounding Variables

The following variables were assessed between the two groups of patients with and without schizophrenia: age (16–25 and 26–35 years), sex, and Charlson Comorbidity Index (CCI). The CCI (18) is a numerically weighted score composed of 17 comorbid conditions: congestive heart failure, chronic pulmonary disease, cerebrovascular disease, dementia, diabetes without complications, liver disease, peptic ulcer disease, peripheral vascular disease, rheumatic disease, hemiplegia or paraplegia, diabetes with complications, malignancy, renal disease, metastatic solid tumor, and HIV/AIDS.

Statistical Analysis

Qualitative variables were expressed as percentages and were first compared between the two groups with and without schizophrenia using the Pearson χ^2 test or Fisher exact test under the conditions of application. Then, multivariate logistic regressions adjusted for age, sex, and CCI scores were performed with backward selection. The results are reported as adjusted odds Ratio (aOR) and 95% CIs.

A sensitivity analysis was performed by a survival analysis using a Cox proportional hazard regression model. Hazard ratios (HRs) and 95% CIs were then estimated after adjustment for potential confounders, using time from index hospitalization to the first acute diabetes complication. Outcomes were measured over a 3-year period after index hospitalization. Individuals were censored at death, development of the outcome of interest, or the latest all-cause hospitalization for people without acute diabetes complications.

The association between hospitalization for suicide attempts and acute diabetes complications was explored, and we adjusted for age, sex, and schizophrenia. The exposure of acute diabetes complications that changes during the epidemiologic follow-up of subjects was

taken into account as a time-dependent covariate in the Cox proportional hazards model. We followed individuals until hospitalization for suicide attempt, death, or the end of the 3-year follow-up period—whichever came first. A *P* value of <0.05 was set a priori to define statistical significance for all analyses. SAS 9.3 software was used for the data analyses.

This study was approved by the French national committee for data protection (registration no. 1576793). Individual written consent was not needed for this study. Data from the PMSI database was provided by the French national agency for the management of hospitalization data (Technical Agency for Information on Hospital Care (ATIH) no. 2015-111111-47-33).

RESULTS

From 2009 to 2012, 45,655 patients aged 15–35 years were hospitalized for type 1 diabetes in France. Among them, 341 (0.75%) had a previous or contemporary hospitalization for schizophrenia. The characteristics of patients with type 1 diabetes at index hospitalization according to the co-occurrence of schizophrenia are given in Table 1. Patients with a history of hospitalization for schizophrenia were more often male and older, with CCI scores ≥ 3, than were people without schizophrenia.

At 1 year (Table 1), individuals with both type 1 diabetes and schizophrenia in comparison with type 1 diabetes alone had been rehospitalized more often for hypoglycemia, hyperglycemia, coma, and ketoacidosis. They were more likely to have experienced at least one of the acute complications. The number of these events (0, 1, 2, or ≥ 3) was significantly different between the two groups for hypoglycemia, hyperglycemia, coma, ketoacidosis, and all acute complications. Individuals with schizophrenia also showed more histories of suicide attempts over the 1-year follow-up period. In addition, hospital mortality was higher for these patients. At 3 years (Table 2), the results were similar, with increased incidence of all diabetes complications, suicide attempts, and hospital death in patients with diabetes with schizophrenia.

After adjustment for age, sex, and CCI scores, logistic regression analyses showed that comorbid schizophrenia among people with type 1 diabetes was associated with increased risks of rehospitalization for all acute diabetes complications within 1 and 3 years from index hospitalization. The results of adjusted logistic regression analyses within 3 years are presented in Table 3. At 3 years, schizophrenia was associated with increased risks of rehospitalization for hypoglycemia, hyperglycemia, ketoacidosis, coma, and suicide attempts but not hospital mortality. However, schizophrenia was associated with hospital mortality after adjustment for sex and age only. The results were consistent at 1 year or after adjustment for age and sex only.

In a multivariate Cox proportional hazards analysis comparing the rate ratio of developing the primary outcomes, adjusted for age and sex, presence of schizophrenia yielded an aHR of 2.17 (95% CI 1.72–2.74) for all acute diabetes complications. The risk was similar when the adjustment included age, sex, and CCI (aHR 2.13 [95% CI 1.69–2.69]).

Finally, after adjustment for sex, age, and schizophrenia, a hospitalization for suicide attempt was associated with an increased risk of hospitalization for acute diabetes complications (aHR 3.46 [95% CI 2.74–4.38]).

Table 1—Characteristics of patients with diabetes with or without schizophrenia and frequency of rehospitalizations for acute diabetes complications, suicide attempts, and hospital mortality over 1- and 3-year follow-up periods

	Schizophrenia (*n* = 341)	No schizophrenia (*n* = 45,314)	*P*
Age (years)			
Mean ± SD	28.7 ± 4.9	26.0 ± 5.8	<0.0001
Median	30	26	
16–25	89 (26.1)	21,161 (46.7)	<0.0001
26–35	252 (73.9)	24,153 (53.3)	
Sex			
Male	233 (68.3)	22,408 (49.4)	<0.0001
Female	108 (31.4)	22,906 (50.5)	
CCI			
1–2	291 (85.3)	42,583 (94.0)	<0.0001
≥3	50 (14.7)	2,731 (6.0)	
1-year follow-up			
At least one instance of hypoglycemia	10 (2.9)	315 (0.7)	0.0002
At least one instance of hyperglycemia	5 (1.5)	81 (0.2)	0.0005
At least one coma	10 (2.9)	351 (0.8)	0.0004
At least one instance of ketoacidosis	31 (9.1)	2,145 (4.7)	0.0003
At least one complication	45 (13.2)	2,678 (5.9)	<0.0001
At least one suicide attempt	19 (5.6)	178 (0.4)	<0.0001
Hospital mortality	7 (2.1)	307 (0.7)	0.007

Data are *n* (%) unless otherwise indicated.

CONCLUSIONS

To our knowledge, this nationwide population-based study is the largest study exploring the increased risk of complications conferred by schizophrenia in young people hospitalized with type 1 diabetes. We found that schizophrenia was associated with a significant increase in rehospitalization for all measured acute diabetes complications (aOR

Table 2—Frequency of rehospitalizations for acute diabetes complications over 3 years of follow-up in patients with diabetes with or without schizophrenia

	Schizophrenia (*n* = 341)	No schizophrenia (*n* = 341)	*P*
At least one instance of hypoglycemia	18 (5.3)	745 (1.6)	<0.0001
At least one instance of hyperglycemia	9 (2.6)	184 (0.4)	<0.0001
At least one coma	16 (4.7)	736 (1.6)	0.0002
At least one instance of ketoacidosis	53 (15.5)	4,338 (9.6)	0.0002
At least one complication	71 (20.8)	5,330 (11.8)	<0.0001
At least one suicide attempt	36 (10.6)	436 (1.0)	<0.0001
Hospital mortality	10 (2.9)	454 (1.0)	0.002

Data are size (%).

Table 3—Logistic regression analyses adjusted for age, sex, and CCI on the risk of selected outcomes at 3 years in patients with type 1 diabetes and with versus without hospitalization for schizophrenia

	Model 1, hypoglycemia	Model 2, hyperglycemia	Model 3, coma	Model 4, ketoacidosis	Model 5, all complications	Model 6, hospital mortality	Model 6b, hospital mortality adjusted for age and sex	Model 7, suicide attempts
Schizophrenia, ref = 0	3.21 (1.99–5.20)	7.01 (3.53–13.90)	3.17 (1.90–5.27)	2.01 (1.49–2.70)	2.21 (1.69–2.88)	—	2.83 (1.50–5.36)	12.15 (8.49–17.38)
Age 16–25 years, ref = 26–35	—	1.94 (1.45–2.60)	1.41 (1.21–1.63)	2.00 (1.87–2.13)	1.82 (1.72–1.93)	—	0.77 (0.64–0.93)	—
Sex, ref = male	—	—	1.20 (1.04–1.39)	—	—	—	—	—
CCI ≥3, ref = 0–1–2	1.46 (1.13–1.89)	2.26 (1.45–3.53)	1.60 (1.24–2.07)	1.16 (1.02–1.33)	1.31 (1.17–1.47)	14.87 (12.34–17.92)	—	—

Data are aOR (95% CI). ref, reference.

2.21), as well as a higher occurrence of suicide attempts (aOR 12.15) and higher hospital mortality (aOR 2.83), at 1 and 3 years of follow-up.

One of the strengths of this study is the population-based design using a French hospital database, which provides detailed epidemiological information on inpatients and allows up to 3 years of follow-up after a hospital stay. Moreover, when our data are compared with prescriptions (data from the French national information system that aggregates hospital discharge abstracts, out-of-hospital care, and long-term illnesses), we can estimate that the individuals included in our study comprise a large proportion of all people with type 1 diabetes aged 15–35 years. Indeed, 45,625 people aged 15–34 years were treated by insulin in 2012 (19). In our study, we included 45,655 individuals from 2009 to 2012, which is probably a slightly higher proportion because some patients aged 15–35 years in 2009 were >35 years old in 2012. The high proportion of inpatients among patients with type 1 diabetes can be explained by French medical practices, as usual care generally includes one hospitalization per year. In addition, the French health insurance authorizes the reimbursement of one hospitalization per year.

It has been reported that the use of hospitalization data is a flawed method for identifying patients with schizophrenia in France (20). However, this bias is probably of limited effect. The potential consequence of this would be an overrepresentation of unidentified cases of schizophrenia in the control group, therefore reducing the amplitude of the reported associations. To further clarify this point, we tried to estimate the proportion of people aged 15–35 years with both schizophrenia and type 1 diabetes in France. Galler et al. (8) reported that 0.48% of people with type 1 diabetes aged <25 years (median age 17.0 years) received antipsychotic medication, bringing the number of people aged 15–35 years with schizophrenia and type 1 diabetes to 249 (using the estimation of 51,800 people aged 15–35 years suffering from schizophrenia in France in 2014) (20). This is below the number of patients reported in our study (n = 341). Overall, we are confident that the total number of patients with schizophrenia among patients with type 1 diabetes reported in our study likely represents the majority of patients with this comorbid condition in the general population. Some limitations also have to be acknowledged. First, we have limited the age of inclusion to between 15 and 35 years old with the objectives both of improving the reliability of type 1 diabetes diagnoses and of limiting the inclusion of the rare forms of very early–onset psychosis. This limits the generalization of findings, although this age-group is possibly the most relevant for the question raised. Imbalances in age and sex between groups may be explained by the well-known earlier age at onset and age at first hospitalization in men relative to women with schizophrenia (21). Second, only hospitalized patients were selected, and those receiving only ambulatory care were therefore not included. Furthermore, diagnoses were carried out in hospitalized patients only. This limitation may raise the question of the representativeness of the population. Regarding diabetes, as highlighted above, most people with type 1 diabetes in France are hospitalized at some point during their medical care. Hence, a majority of patients with type 1 diabetes were likely included in the current study. A second issue is that our results do make it possible to conclude that patients with schizophrenia experience more diabetes complications. Indeed, it could be hypothesized that these individuals are sometimes hospitalized for light glycemic imbalance because of their psychiatric status (e.g., the physician may be worried that the patient will not be able to handle this problem alone), while the same problem is handled in outpatient care in patients without mental health issues. Our results should therefore be interpreted as a higher risk of hospitalization for complications in these patients. However, the fact that more coma and higher hospital mortality rates were also found in patients with schizophrenia suggests that, beyond hospitalization, this comorbidity increases the risk of very severe complications and a lethal outcome. Third, diagnoses were extracted from hospital discharge abstracts, but the quality of these diagnoses cannot be assured. Fourth, we were unable to explore the motives of the reported associations between schizophrenia and diabetes complications, hospital mortality, or suicide attempts. Notably, we were not able to

differentiate the effect of schizophrenia from the effect of psychotropic medication or compliance with treatment because this information was not available. Antipsychotic medication may affect metabolic control and insulin action and, therefore, increase the risk of severe acute complications. Unfortunately, we do not have details about antipsychotic intake in individuals here. Finally, data about out-of-hospital mortality were not available. It cannot be excluded that individuals with both diabetes and schizophrenia who experience complications die prior to admission more often than individuals with diabetes who are not schizophrenic. In this case, our report of higher hospital mortality rates in patients with diabetes with schizophrenia probably underestimates the risk of death due to diabetes complications in those with schizophrenia. Few studies have investigated the effects of schizophrenia in type 1 diabetes. Our results are nevertheless consistent with and extend the results of a previous American study (14). In 82,060 patients with either type 1 or 2 diabetes hospitalized in 2010–2011 in Washington state, 0.52% had comorbid type 1 diabetes and schizophrenia, which is slightly lower than in our study. Early rehospitalization (within 1 month) for medical complications was more common in those with severe mental illness, a risk persisting over 24 months. Other studies have explored the risk of diabetes complications in the case of concomitant schizophrenia but usually did not assess the specific effect of type 1 diabetes (e.g., ref. 6).

The mechanisms explaining the increased risk of somatic complications in schizophrenia could not be assessed here. It is possible that, as for type 2 diabetes, multiple factors are involved. For instance, our results showed ketoacidosis to be the most common complication (9–15.5% of patients with type 1 diabetes), with some patients presenting with multiple episodes. This complication, which is very common in youths, is the result of absolute insulin deficiency and is often caused by insulin under dosing or discontinuation of treatment. Treatment noncompliance has various causes (22). However, some studies suggest that patients with schizophrenia tend to have good adherence to diabetes treatments (23). An alternative explanation may be related to health professionals and the care system (24). For instance, an Australian study showed that patients with psychotic disorders had a lower probability of having the recommended HbA_{1c}, lipid profile, or microalbuminuria tests and a higher risk of hospitalization for diabetes complications and diabetes-related or all-cause mortality (25,26). In schizophrenia, in spite of their knowledge of the acute and long-term risks conferred by diabetes (8), psychiatrists may therefore be more focused on psychiatric symptoms than on comorbid somatic disorders. Other causes of poor diabetes control in schizophrenia may include poor diet and lack of physical activity (27). Individuals with both schizophrenia and type 1 diabetes may represent a particularly vulnerable population at risk for both somatic and psychological issues.

According to the American Diabetes Association, inpatient care constitutes the highest proportion of medical expenditures for diabetes (28). It is well-known that the heavy economic burden of diabetes on the health care system increases early during the course of the disease, notably in relation to rehospitalization for acute complications. In France, the hospitalization rates (based on diagnosis-related groups) are higher when a patient with diabetes has schizophrenia regardless of whether he/she is admitted for severe hypoglycemia (doubled), coma, or ketoacidosis (50% higher). As a consequence, even though the patient population with type 1 diabetes/schizophrenia is small, it requires substantially more from the health care system.

Our study also showed an increased risk of suicide attempts in hospitalized patients with schizophrenia and type 1 diabetes. Both diabetes and schizophrenia are independently associated with increased risks of suicide attempts. In a study of adolescents with type 1 diabetes, 0.8% had attempted suicide versus 0.4% in healthy control subjects (29). This second statistic is similar to what was reported here for patients with no schizophrenia (0.98%). Moreover, almost 30% of patients with schizophrenia have a personal history of at least one suicide attempt (30). Our study showed that schizophrenia yields a 12-fold increase in the risk of suicide attempts among patients with type 1 diabetes over a 3-year period. It is worth noting that suicide attempts and diabetes complications were associated independently from schizophrenia, suggesting that common factors may contribute to both risks in patients with type 1 diabetes. For instance, low impulse control has been associated with both worse diabetes management in type 1 diabetes (31) and higher suicide rates in schizophrenia (32). This needs to be more specifically investigated. An alternative explanation may be that some diabetes complications, for instance, insulin overdoses or lack of compliance, are an expression of suicidal tendencies in some patients. Overall, diabetes complications and suicide attempts may be markers of more severe physio- and psychopathology in a subset of patients, notably, but not only, in those with schizophrenia.

In conclusion, our study showed that among patients with type 1 diabetes, patients with schizophrenia present an increased risk of hospitalization for diabetes complications, suicide attempts, and hospital mortality. While this comorbidity occurs in $<1\%$ of the population of young patients hospitalized with type 1 diabetes, it is a significant factor of morbidity and mortality. This excessively fragile subgroup of patients may require specific care programs combining the joint action of teams specialized in diabetes and schizophrenia and close monitoring of mental, somatic, and social heath.

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