**Objectives:** To fully ascertain the familial aggregation of restless legs syndrome (RLS) and to characterize the clinical features of familial RLS (fRLS) cases.

**Design:** A case series survey with a high response rate.

**Setting:** Academic research center.

**Participants:** Consecutive RLS probands (n = 249) were followed up in a specialized sleep center for 15 years. A total of 671 cases of fRLS met the current standard diagnostic criteria, including 192 probands characterized using multidimensional clinical assessments and 479 affected family members assessed by their responses to a structured questionnaire telephone diagnostic interview.

**Main Outcome Measures:** Sibling and offspring relative risk ratio and clinical and genetic features of patients with fRLS and families.

**Results:** Our data showed that RLS aggregates in families with a familial rate of 77%, a sibling relative risk of 3.6 (95% confidence interval, 2.8-4.4), and an offspring relative risk of 1.8 (1.0-2.7). Familial RLS is a chronic disorder with a mean (SD) disease duration of 24 (16) years and a wide range of age of onset (mean [SD], 28 [15] years), with most family members having early-onset disease but mild to moderate RLS symptoms. Our clinical data also indicated that fRLS is more prominent among women who also had increased incidence of anemia/iron deficiency, arthritis, and number of pregnancies. Pregnancy-related RLS seems to be a characteristic feature of fRLS, and afflicted women tend to have a much younger age of onset.

**Conclusions:** Restless legs syndrome significantly aggregated in families with variable phenotypic expressivity, and the siblings of severely affected individuals have an increased risk of developing the disease.

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**METHODS**

All RLS probands were consecutively recruited, ascertained, and sampled through the Centre of Sleep and Biological Rhythms Study, mostly between September 1993 and December 2008. The detailed ascertainment strategy, clinical assessments, and diagnostic criteria applied to the diagnosis of the RLS probands have been previously described.

**QUESTIONNAIRE, TDI, AND FAMILY STUDY**

A standardized questionnaire (eFigure, http://www.archneurol.com) was first conducted for each proband, either face to face or via tele-
phone, during or right after the first appointment at the sleep clinic. Ten items for the determination of the severity score (as defined by the International RLS Study Group [IRLSSG]) were added to the questionnaire in 2002. Each proband or the designated most knowledgeable family informant provided a complete pedigree with detailed genealogical information, complete sibships, birth order of each family union, family history of RLS symptoms, and a brief medical history for all first-, second-, and, when possible, third-degree and remote relatives. They also supplied a list of available family members and their contact information. An experienced clinical research associate (P.T.) trained at the sleep clinic then conducted all the interviews by telephone for all available adult family members (≥18 years old) using the same questionnaire. Each TDI usually takes about 45 to 60 minutes to complete. The family history and pedigree structure of each family were verified by at least 1 other informant.

The study was approved by all involved institutional ethical committees. All participants provided verbal consent for the TDIs.

DIAGNOSIS AND CLASSIFICATION OF RLS

All symptomatic individuals who fulfilled the 4 essential diagnostic criteria based on the answers provided during the TDIs were classified as having definite RLS, whereas individuals missing 1 of the mandatory diagnostic criteria but having 1 or more supporting attributes of an RLS diagnosis were classified as having probable RLS. All probands had an RLS diagnosis based on their responses on the questionnaire, which was compatible with their clinical diagnosis by multidimensional clinical assessments. Family members with uncertain diagnoses (eg, missing >1 essential clinical criterion or with a total illness duration of less than 6 months) and symptomatic individuals who did not complete the clinical investigation or TDI were considered to have possible RLS and were excluded from the subsequent analyses. Family members who denied having any RLS symptoms according to their relatives but were not screened by TDI were classified as said- unaffected and were excluded from the subsequent analyses as well. Only those family members (≥18 years old) negative for both “urge to move” and “discomfort in the legs” as assessed by TDI were classified as unaffected at the time of investigation.

The proband was classified as having RLS when there was at least 1 first-degree relative with an RLS diagnosis confirmed directly or indirectly (mean [SD] pedigree size, 12 [10] individuals per family), which included 567 sibships (mean [SD] size, 4 [3] siblings per sibship). A detailed distribution of different categories, for a total of 2729 family members and their clinical status, are shown in Table 1. Among the 1350 living adult biological relatives with contact information, 5.0% could not be reached, and 10.0% declined to participate in the study; therefore, the response rate for the TDI survey was 85.0%. Although all probands were from Montreal, only 30.0% of their family relatives lived in Montreal and surrounding areas, with the remaining 60.0% living in Quebec City and surrounding areas and 10.0% living outside of Quebec in Canada or abroad.

Among the 1141 individuals (249 probands and 892 living adult relatives) who completed the questionnaire, 194 men and 200 women had never had any RLS symptoms and were therefore considered to be unaffected; another 268 men and 479 women were symptomatic (ie, definitely or probably affected) for RLS (female to male ratio, 1.79; χ² = 18.74; P < .001). A total of 367 patients with RLS (69% women) completed the severity scale according to the criteria of the IRLSSG. To our knowledge, this study represents the largest collection of full-family study data on RLS so far reported in the literature.

STATISTICAL ANALYSES

All descriptive statistics and between-group comparisons were performed using STATISTICA statistical software (StatSoft Inc, Tulsa, Oklahoma). The comparison of means for continuous variables was performed using 2-tailed equal-variance t tests, and the comparison of dichotomous variables was performed using 2-tailed Fisher exact tests with 2 × 2 contingency tables or using 2-tailed χ² tests if the comparisons included more than 2 variables. Correlation analyses were performed using 2-tailed Pearson tests. In addition, 20 quantitative variables were compared between groups, including age, age at onset, duration of illness, 10 individual items on the severity scale and the total severity scale, number of associated conditions, measurements of periodic leg movements during sleep (PLMS) and periodic leg movements while awake (PLMw), Suggested Immobilization Test (SIT) scores, and sleep latency and efficiency. For single tests, P < .05 was considered significant; for the comparison of multiple variables between groups, the Bonferroni correction was applied for multiple testing. Multigroup univariate comparisons were performed using analysis of variance.

The relative sibling recurrence risk (λs) and the offspring recurrence risk (λo) were calculated as the ratio of the recurrence risk in the living adult siblings and offspring of the probands vs the population prevalence estimated in the literature (ie, 10%), which corresponds to a type II relative risk. Only living adult siblings and offspring screened by questionnaire were included in the calculation of λ. Family structure statistics were generated by PEDINFO, which is part of the SAGE statistical software package, version 5.2.0 (SAGE Project, Case Western Reserve University, Cleveland, Ohio).

RESULTS

SUMMARY OF THE FAMILY STUDY

A total of 249 probands and their relatives were interrogated directly or indirectly (mean [SD] pedigree size, 12 [10] individuals per family), which included 567 sibships (mean [SD] size, 4 [3] siblings per sibship). A detailed distribution of different categories, for a total of 2729 family members and their clinical status, are shown in Table 1. Among the 1350 living adult biological relatives with contact information, 5.0% could not be reached, and 10.0% declined to participate in the study; therefore, the response rate for the TDI survey was 85.0%. Although all probands were from Montreal, only 30.0% of their family relatives lived in Montreal and surrounding areas, with the remaining 60.0% living in Quebec City and surrounding areas and 10.0% living outside of Quebec in Canada or abroad.

FAMILIAL AGGREGATION OF RLS

Among the 249 fully investigated probands, 192 (77.1%) were classified in the IRLS1 group and another 57 (22.9%) were classified as sRLS, as previously defined. An additional 479 family members from 192 pedigrees who com-
completed the TDI and fulfilled the diagnostic criteria were classified as the fRLS2 group.

The sibling (mean [SD] age, 57 [12] years) relative risk was 3.6 (95% confidence interval, 2.8-4.4) and the offspring (mean [SD] age, 36 [12] years) relative risk was 1.8 (1.0-2.7). Both were calculated using an estimated population prevalence of 10%.

Among the 192 fully studied families, 76 had only 1 symptomatic individual, 83 had 2 to 5 symptomatic individuals, 21 had 6 to 10 symptomatic individuals, and 12 had more than 10 symptomatic individuals. Visual inspection of the pedigrees presenting the RLS phenotype indicated that most of the pedigrees (~90%) showed a vertical transmission compatible with a dominant-like inheritance pattern; however, some pedigrees were compatible with recessive inheritance. Among the 567 nuclear families ascertained, we observed some cases of distortion of Mendelian inheritance, ie, 38 nuclear families had 50% or more of siblings symptomatic with ascertainment of complete sibship. Among the 567 nuclear families in the study, 16 nuclear families also had biallelic inheritance (ie, both parents were affected and/or had a positive family history), among which 50% or more of siblings in 8 nuclear families were symptomatic.

**GENERAL CLINICAL CHARACTERISTICS OF FAMILIAL RLS**

The collective main clinical features of these 671 fRLS cases are summarized as follows.

**Sex Differences**

Our data confirmed that more women had fRLS (447 women vs 224 men), particularly among the first-degree relatives, as shown in Table 1. The 3 main associated medical conditions for women with RLS were anemia, arthritis, and pregnancy (37% women) (eTable 1). Women with fRLS tended to have a higher total severity score compared with men (P = .001), although the main differences regarding the self-estimated general severity (P < .001), daily severity (P < .001), and mood disturbance (P = .001). In contrast, scores on other items of the severity scale were similar between women and men with fRLS. Women also had lower mean PLMS measurements (P = .001), whereas SIT, PLMW, sleep latency, and efficiency scores were similar in the 2 groups. There was no difference regarding the number of pregnancies between RLS symptomatic vs asymptomatic women (mean [SD], 2.4 [2.3] vs 2.7 [2.2]; P = .17). However, women with fRLS for whom the RLS symptoms either appeared for the first time or were aggravated during their pregnancies had more children than women with pregnancy-unrelated RLS (mean [SD], 3.5 [2.8] vs 2.6 [1.8]; P = .004), for whom RLS symptoms appeared well after pregnancy or remained unchanged during pregnancy. Women with pregnancy-related RLS symptoms also had a much younger mean (SD) age at onset (20.7 [7.4] vs 32.6 [15.9] years; P < .001) and longer illness duration (mean [SD], 33.1 [15.9] vs 22.5 [16.1] years; P < .001) compared with women with pregnancy-unrelated RLS.

**Age at Investigation, Age at Onset, and Disease Duration**

The age at investigation was close to a normal distribution, with a mean age among the whole fRLS cohort of 52.0 years (Figure, A). The distribution of age at onset was skewed, with the mean for fRLS being 28.0 years and the peak happening around 11.0 to 20.0 years (Figure, B). The mean (SD) illness duration was 24.0 (16.0) years (95% confidence interval for the mean, 22.5-25.0 years; range, 1.0-78.0 years). Most patients with fRLS had experienced RLS symptoms for most of their lives. Among all the RLS pedigrees studied, there were 109 nuclear families consisting of 198 affected parent-offspring pairs. The mean (SD) age at investigation, age at onset, and duration of illness for the parental generation were 64.8 (12.0) years, 30.7 (17.2) years, and 33.8 (16.9) years, respectively, compared with the offspring generation (42.0 [14.1] years, 23.4 [11.5] years, and 18.4 [14.1] years, respectively). The difference of age at onset (~6.3 [18.7] years) between the parental and offspring generations was significant (P < .001). However, the parental generation had a higher mean (SD) severity score compared with the offspring generation (21.8 [8.0] vs 19.5 [7.8]; P = .046). A correlation analysis also indicated that age at onset was highly correlated with age at investigation (r = 0.432;

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**Table 1. Clinical Status of RLS in 2729 Family Members From 249 RLS Families**

<table>
<thead>
<tr>
<th>Family Member</th>
<th>Definitely Affected</th>
<th>Probably Affected</th>
<th>Possibly Affected</th>
<th>Said-Unaffected</th>
<th>Unaffected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated spouses</td>
<td>16 (5.0)</td>
<td>3 (0.9)</td>
<td>10 (3.1)</td>
<td>222 (69.6)</td>
<td>68 (21.3)</td>
<td>319</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>258 (13.4)</td>
<td>54 (2.8)</td>
<td>303 (15.7)</td>
<td>1127 (58.4)</td>
<td>188 (9.7)</td>
<td>1830</td>
</tr>
<tr>
<td>Father</td>
<td>6 (2.4)</td>
<td>1 (0.4)</td>
<td>73 (29.6)</td>
<td>149 (60.3)</td>
<td>18 (7.3)</td>
<td>247</td>
</tr>
<tr>
<td>Mother</td>
<td>18 (7.3)</td>
<td>4 (1.6)</td>
<td>63 (25.5)</td>
<td>144 (58.3)</td>
<td>18 (7.3)</td>
<td>247</td>
</tr>
<tr>
<td>Sister</td>
<td>114 (21.9)</td>
<td>25 (4.8)</td>
<td>45 (8.6)</td>
<td>274 (52.6)</td>
<td>63 (12.1)</td>
<td>521</td>
</tr>
<tr>
<td>Brother</td>
<td>67 (12.4)</td>
<td>9 (1.7)</td>
<td>71 (13.1)</td>
<td>345 (63.7)</td>
<td>50 (9.2)</td>
<td>542</td>
</tr>
<tr>
<td>Son</td>
<td>20 (10.2)</td>
<td>8 (4.1)</td>
<td>33 (16.8)</td>
<td>120 (60.9)</td>
<td>16 (8.1)</td>
<td>197</td>
</tr>
<tr>
<td>Daughter</td>
<td>33 (18.8)</td>
<td>7 (4.0)</td>
<td>18 (10.2)</td>
<td>95 (54.0)</td>
<td>23 (13.1)</td>
<td>176</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>99 (27.1)</td>
<td>21 (5.8)</td>
<td>39 (10.7)</td>
<td>108 (29.6)</td>
<td>96 (26.8)</td>
<td>365</td>
</tr>
<tr>
<td>Third-degree and remote relatives</td>
<td>33 (28.7)</td>
<td>14 (12.2)</td>
<td>7 (6.1)</td>
<td>21 (18.3)</td>
<td>40 (34.8)</td>
<td>115</td>
</tr>
</tbody>
</table>

Abbreviation: RLS, restless legs syndrome.

aData are given as the number of individuals in each category (percentage of each class of relatives). Percentages may not sum to 100 because of rounding.
Therefore, the earlier age at onset observed in the offspring generation may be related to heightened awareness of disease symptoms within a family.

**Different Clinical Courses**

Of fRLS cases, 8.0% (mainly family relatives) reported that their RLS symptoms remitted at the time of investigation, 15% reported diminished symptoms, 41% reported stable symptoms, and 36% had progressive symptoms. None of the categorical clinical variables was deterministic of the type of clinical course (data not shown). Multivariate analysis of variance indicated the absence of differences in terms of age, age at onset, disease duration, and sleep measurements among the 4 different types of clinical courses (data not shown).

**Severity**

Three hundred sixty-seven fRLS cases completed the IRLSSG severity scale. Among them, 12% had a very severe score (range, 31-40; mean[SD], 34[2]), 34% had a severe score (21-30; 25[3]), 43% had a moderate score (11-20; 15[3]), and 11% had a mild score (8-10; 8[2]). None of the clinical variables was deterministic of the different degrees of severity solely (data not shown).

**CLINICAL CHARACTERISTICS OF DIFFERENT SUBGROUPS**

**Familial vs Sporadic RLS Probands**

The comparison of the clinical features of the 192 fRLS probands with those of the 57 sRLS probands revealed that the most significant differences between the fRLS1 and sRLS groups were a significantly younger age at onset for the former, as previously reported,5,20 a relatively longer duration of the disease, and slightly higher PLMS measurements (Table 2). However, the familial probands have larger sibship (mean[SD], 4.8[3.3] siblings per sibship) compared with the sporadic probands (3.9[3.2] siblings per sibship) (P=.01, t test), whereas the numbers of uninterviewed siblings in familial vs sporadic groups are not different (3.9[3.0] vs 3.3[3.0]; P=.46, t test). Therefore, the designation of familial vs sporadic groups may be largely influenced by the family size itself.

**Familial RLS Probands vs Affected Relatives**

The comparison of the 192 fRLS probands with the 479 fRLS family members (ie, fRLS1 vs fRLS2) did not reveal a significant difference of age at investigation and duration of illness between these 2 groups, with similar early age at onset (Table 2) in both groups. However, the proband group had much higher scores on individual items of the IRLSSG severity scale and total severity scale than the relatives group. Moreover, there were no differences in SIT, PLMS and PLMW measurements, and sleep latency between the proband and relatives groups. There was no significant difference for the presence of associated medical conditions between the fRLS probands and the affected relatives (eTable 2). However, we observed a much higher rate of restless arms in the probands compared with the relatives (P<.001). The profiles of clinical course and severity were significantly different in probands and affected relatives (P<.001 for both comparisons). Most probands were considered to be severe RLS cases with profound sleep problems (eTable 2), which could be owing, at least partially, to the fact that these patients came to a sleep clinic for medical consultation and treatment.

**COMMENT**

Restless legs syndrome is one of the few common neurological disorders that exhibit significant familial aggregation. The dissection of the underlying genetic and nongenetic composition of the outstanding familial aggregation observed in RLS should be interesting to all concerned physicians, geneticists, and epidemiologists. Our data have further confirmed the significant familial aggregation of RLS, as evidenced by the strong positive family history (77%), the significantly increased sibling relative risk (λs=3.6; 93%
et al28 used a simple statistical model to demonstrate that familiality can be attributed to either genetic or environmental risk factors, or a combination of both. Khoury and coworkers29 recently suggested that the pregnancy-related RLS symptoms are part of the clinical features of fRLS instead of a form of secondary RLS as previously suggested. The predominance of women with RLS could be explained by a combination of several factors, such as the presence of comorbid conditions (especially the iron-depletion conditions30 such as pregnancy-related RLS) and a higher sensitivity to RLS symptoms (particularly the sensory symptoms) and to the distress that RLS symptoms impose on the lives of female patients. The lower PLMS index in women compared with men with RLS found in this study is intriguing but needs further investigation. It may suggest a different clinical profile in women than in men in terms of their sensory and motor manifestations of RLS.

Another limitation of our study is that we did not design specific questions to eliminate the possible mimics that could fulfill the 4 criteria during the interview, as recently suggested by Hening et al.29 Nevertheless, we expect the percentage of such cases will be very small in our cohort because of our more detailed questionnaire and rigorous diagnostic criteria applied.

Our data have further confirmed the female preponderance of RLS in a large cohort of familial cases and suggested that the pregnancy-related RLS symptoms are part of the clinical features of fRLS instead of a form of secondary RLS as previously suggested. The predominance of women with RLS could be explained by a combination of several factors, such as the presence of comorbid conditions (especially the iron-depletion conditions such as pregnancy-related RLS) and a higher sensitivity to RLS symptoms (particularly the sensory symptoms) and to the distress that RLS symptoms impose on the lives of female patients. The lower PLMS index in women compared with men with RLS found in this study is intriguing but needs further investigation. It may suggest a different clinical profile in women than in men in terms of their sensory and motor manifestations of RLS.

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Correspondence: Guy A. Rouleau, MD, PhD, Center of Excellence in Neuromics, CHUM Research Center and the Department of Medicine, University of Montreal, 1560, rue Sherbrooke E, Room Y-3616-2, Montréal, Quebec H2L 4M1, Canada.

Author Contributions: Drs Xiong and Rouleau had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Table 2. Comparison of Familial and Sporadic RLS

<table>
<thead>
<tr>
<th></th>
<th>Familial RLS</th>
<th>sRLS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proband</td>
<td>Affected Relatives</td>
<td>Proband</td>
</tr>
<tr>
<td>No. of participants</td>
<td>192</td>
<td>479</td>
<td>57</td>
</tr>
<tr>
<td>Age, y</td>
<td>53 (12)</td>
<td>51 (17)</td>
<td>51 (12)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>28 (15)</td>
<td>28 (15)</td>
<td>36 (15)</td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>25 (14)</td>
<td>23 (17)</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Severity score2)</td>
<td>85</td>
<td>255</td>
<td>27</td>
</tr>
<tr>
<td>No. of participants</td>
<td>. . . .</td>
<td>. . . .</td>
<td>85</td>
</tr>
<tr>
<td>Discomfort</td>
<td>3.5 (0.9)</td>
<td>2.9 (1.1)</td>
<td>3.0 (1.2)</td>
</tr>
<tr>
<td>Need to move</td>
<td>3.7 (0.6)</td>
<td>3.4 (1.1)</td>
<td>3.7 (0.8)</td>
</tr>
<tr>
<td>Relieved by activity</td>
<td>1.2 (0.5)</td>
<td>1.2 (0.7)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>3.1 (1.3)</td>
<td>1.7 (1.6)</td>
<td>2.1 (1.7)</td>
</tr>
<tr>
<td>Fatigue and somnolence</td>
<td>2.2 (1.6)</td>
<td>1.2 (1.5)</td>
<td>1.7 (1.6)</td>
</tr>
<tr>
<td>Frequency</td>
<td>3.3 (1.1)</td>
<td>2.1 (1.4)</td>
<td>2.6 (1.3)</td>
</tr>
<tr>
<td>General severity</td>
<td>3.1 (1.1)</td>
<td>2.4 (1.3)</td>
<td>2.7 (1.2)</td>
</tr>
<tr>
<td>Daily severity</td>
<td>2.3 (1.1)</td>
<td>1.6 (0.9)</td>
<td>2.0 (1.1)</td>
</tr>
<tr>
<td>Impacts daily activity</td>
<td>1.9 (1.7)</td>
<td>0.7 (0.1)</td>
<td>1.5 (1.7)</td>
</tr>
<tr>
<td>Mood disturbance</td>
<td>1.8 (1.5)</td>
<td>0.8 (1.2)</td>
<td>1.2 (1.5)</td>
</tr>
<tr>
<td>Total severity score</td>
<td>26.2 (7.1)</td>
<td>18.2 (7.4)</td>
<td>21.7 (8.6)</td>
</tr>
<tr>
<td>Sleep study</td>
<td>. . . .</td>
<td>. . . .</td>
<td>. . . .</td>
</tr>
<tr>
<td>No. of participants</td>
<td>159</td>
<td>23</td>
<td>53</td>
</tr>
<tr>
<td>SIT, index/h</td>
<td>56.7 (56.7)</td>
<td>59.9 (69.0)</td>
<td>65.5 (64.8)</td>
</tr>
<tr>
<td>PLMS, index/h</td>
<td>34.5 (30.2)</td>
<td>32.9 (33.9)</td>
<td>22.5 (23.7)</td>
</tr>
<tr>
<td>PLMW, index/h</td>
<td>59.1 (37.8)</td>
<td>60.5 (24.0)</td>
<td>56.8 (47.0)</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>31.8 (58.7)</td>
<td>12.1 (5.4)</td>
<td>25.0 (33.0)</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>73.5 (18.8)</td>
<td>85.5 (10.6)</td>
<td>77.3 (20.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, not applicable; IRLS, familial RLS; PLMS, periodic leg movements during sleep; PLMW, periodic leg movements while awake; RLS, restless legs syndrome; SIT, Suggested Immobilization Test; sRLS, sporadic RLS.

a Data are presented as the mean (SD), unless otherwise indicated.

b P < .003 was considered significant because of the multiple tests. Boldface signifies statistically significant difference.
for the integrity of the data and the accuracy of the data analysis. Study concept and design: Xiong, Montplaisir, Turecki, Desaultes, and Rouleau. Acquisition of data: Xiong, Levchenko, Thibodeau, and Desaultes. Analysis and interpretation of data: Xiong, Montplaisir, and Dubé. Drafting of the manuscript: Xiong. Critical revision of the manuscript for important intellectual content: Xiong, Montplaisir, Desaultes, Turecki, Gaspar, and Rouleau. Statistical analysis: Xiong, Barhdadi, and Dubé. Administrative, technical, and material support: Thibodeau.

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Additional Contributions: Ridha Joober, MD, PhD, Department of Psychiatry, McGill University, provided advice on general statistical analyses and the use of the STATISTICA program. We thank all the patients and their families; without their participation and full collaboration this study would not be possible.

REFERENCES


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