Prevalence of Fabry Disease and Outcomes in Young Canadian Patients With Cryptogenic Ischemic Cerebrovascular Events

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Background and Purpose—Previous studies reported Fabry disease in 0% to 4% of young patients with cryptogenic ischemic stroke (IS). We sought to determine the prevalence of Fabry and outcomes among young Canadians with cryptogenic IS or transient ischemic attack (TIA).

Methods—We prospectively enrolled individuals aged 18 to 55 with IS or speech or motor TIA, and no cause identified despite predetermined investigation. α-galactosidase-A gene was sequenced for Fabry diagnosis. National Institutes of Health Stroke Scale score was measured at presentation to quantify stroke severity. Modified Rankin Scale determined functional outcomes ≤7 days after presentation and 6 months later.

Results—We enrolled 365 patients with IS and 32 with TIA. α-galactosidase-A sequencing identified a single carrier of a genetic variant of unknown significance (p.R118C) and no well-recognized pathogenic variants. Mean National Institutes of Health Stroke Scale score was 3.1. Proportion of patients with modified Rankin Scale of 0 to 2 was 70.7% at ≤7 days and 87.4% at 6 months. National Institutes of Health Stroke Scale score at presentation and diabetes mellitus predicted 6-month modified Rankin Scale. Thirteen patients experienced 3 recurrent IS and 9 TIA during follow-up. No patient died. Most patients (98.7%) returned home. Among previous workers, 43% had residual working limitations.

Conclusions—In this Canadian cohort of patients with cryptogenic IS or TIA, the prevalence of Fabry was 0.3% if p.R118C variant is considered as pathogenic. This suggests that more cost-effective methods should be applied for diagnosis of Fabry rather than systematic genetic screening in this population. Overall, cryptogenic IS in young adults is associated with favorable outcomes. (Stroke. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.016083.)

Key Words: Fabry disease • outcome • prevalence • speech
variants that differ from the functional wild-type α-GAL-A gene. Some variants are known to be pathogenic, others are disease neutral or nonpathogenic, but many are genetic variants of unknown significance (GVUS).a

Limited information is available on the prevalence of Fabry disease among patients with a cryptogenic stroke from North America. We therefore conducted the CFSSI (Canadian Fabry Stroke Screening Initiative), a large prospective multicenter cohort study of young Canadians with cryptogenic stroke or TIA undergoing predetermined etiologic investigation and follow-up.

Our aim was 2-fold: (1) to determine the proportion of individuals with pathogenic variants or GVUS in the α-GAL-A gene and (2) to report clinical outcomes among young Canadians with cryptogenic IS or TIA.

Methods

Study Population

The CFSSI protocol was previously published. Patients aged 18 to 55 years with acute IS confirmed by neuroimaging or speech or motor TIA lasting ≥10 minutes were prospectively identified from 16 tertiary stroke centers from across Canada. Those with cryptogenic cause were eligible, as defined by predetermined investigations (cerebrovascular imaging, echocardiography, Holter, and prothrombotic workup) documenting no significant artery disease (eg, atherosclerosis with ipsilateral >70% extracranial stenosis or >50% intracranial stenosis, artery dissection, and fibromuscular dysplasia), cardiomyopathic conditions (eg, valvular heart disease and patent foramen ovale combined with atrial septal aneurysm), evidence of paradoxical embolism, acute lacunar infarcts (deep location and <15 mm diameter) related to traditional vascular risk factors (dyslipidemia, hypertension, and diabetes mellitus), antiphospholipid syndrome, or other well-determined causes. Patients were enrolled ≤6 months after qualifying events. Patients with incomplete investigation and those who declined participation were excluded.

Participants underwent clinical evaluation. National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) were determined from chart abstraction and direct interview. A follow-up interview was conducted 6 months after qualifying events. Patients with incomplete investigation and those who declined participation were excluded.

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Fabry Screening

Blood samples were sent to the designated study laboratory at the University of Rostock, Germany (http://albrecht-kossel-institut.de) for Fabry screening by direct sequencing of the α-GAL-A gene. Positive screens included any genetic variant labeled as pathogenic or GVUS.a Participants with positive screens were referred to specialized centers participating in the Canadian Fabry Disease Initiative for further investigation, including measurement of lyso-Gb3 level, and clinical management as per Canadian Fabry Disease Initiative guidelines.

Statistical Analysis

Descriptive analysis of the participants’ baseline characteristics and outcomes was conducted. Means with SDs, medians, and selected percentiles were described for continuous data. Prevalence of positive Fabry screens and other categorical data was reported with observed frequencies and percent. Wilson method was used to construct 95% confidence intervals (CIs) of differences in proportions. A multivariable logistic regression model was used to examine the association between a priori clinically relevant variables and the outcome of interest, good (mRS score of 0–2) versus poor (mRS score of 3–6) outcome at 6 months. Because of sample size considerations, the number of covariates was restricted to 4, and were a priori specified based on clinical relevance as age, sex, presence of diabetes mellitus, and NIHSS score. A restricted cubic spline with 3 knots was used for NIHSS score. Calibration of the model was checked using bootstrap techniques and visual plots. Models were validated using the bootstrap. A 2-sided P value of <0.05 was considered statistically significant.

Ethical Considerations

The CFSSI protocol was approved by the Research Ethics Boards at St. Michael’s Hospital, Toronto, Centre hospitalier de l’Université de Montréal, Montreal, and each study site before recruiting study participants. Participants signed informed consent forms before collection of data and blood samples for the CFSSI.

Results

From 426 potential study participants, 7 were deceased or lost to contact pre-enrollment, and 22 declined study participation, leaving 365 patients with IS and 32 with TIA as qualifying events. This corresponded to a study population coverage of 93.2% (397/426).

Table 1 shows baseline demographics, clinical features, and investigation for the entire study cohort and by age group (<45 versus ≥45 years). Before admission, 98.5% of patients were living at home and 85.9% were actively working. Vascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking (ever), and alcohol abuse) and preadmission use of antiplatelet and antihypertensive agents were more frequent in patients aged ≥45 years. One third of patients had isolated patent foramen ovale. Neurological manifestations of the index event included hemiparesis (71.5%), hypesthesia (53.7%), dysarthria (42.8%), ataxia (32.5%), aphasia (29.0%), vertigo (17.6%), and diplopia (12.3%). Headache was more common among the younger group (39.4% versus 26.6%; P=0.01).

IS severity was generally low (mean NIHSS score of 3.4±2.3) and did not differ between sex or age groups. For most of the 365 IS patients, the qualifying stroke mechanism was nonlacunar (84.0%) primarily affecting cerebral hemispheres (69.1%), especially among patients aged ≥45. Compared with those with IS as a qualifying event, more TIA patients had suffered previous cerebrovascular events (38% versus 11%; P<0.001) and were receiving antiplatelet agents at presentation (25% versus 11%; P=0.04).

Positive Fabry Screens

From our cohort, 8 of 395 young patients with cryptogenic ischemic events screened positive for Fabry (Table 2), corresponding to a 2.0% prevalence (95% CI, 1.0%–3.9%). These included 7 of 363 IS patients (1.9%) and 1 of 32 TIA patients (3.1%). None had a classical early-onset clinical Fabry phenotype. Positive screening included no variants known to cause Fabry (95% CI, 0.0%–1.0%). There were 6 patients with multiple genetic variants that were ultimately considered to be disease neutral after referral through the Canadian Fabry Disease Initiative. A seventh patient, a 39-year-old heterozygous female with a single disease-neutral variant (p.D313Y), presented with dysarthria and right-sided sensory deficit (NIHSS score of 2). Brain magnetic resonance imaging identified an acute left thalamic lacune and no previous infarct or leukoaraiosis. Computed tomographic angiography documented basilar
fenestration, but no vertebrobasilar dolichoectasia or other artery disease. Blood tests documented normal creatinine and lyso-Gb3 level (0.7 ng/mL; normal ≤ 0.9). First-degree family assessment through Canadian Fabry Disease Initiative revealed no suspected Fabry. Her mRS improved from 2 at baseline to 1 at 6 months and 0 after 26 months of follow-up, with no recurrent cerebrovascular event on aspirin and atorvastatin prophylaxis. The eighth patient with positive screen was a 55-year-old hemizygous male with a GVUS (p.R118C). He presented with mild aphasia, dysarthria, and paresis (NIHSS score of 3). Brain magnetic resonance imaging revealed a left basal ganglia and subcortical infarctions. Vascular imaging and transesophageal echocardiography were unremarkable. Creatinine was normal. Blood lyso-Gb3 was at 0.48 ng/mL (normal ≤ 0.9). He had no further cerebrovascular event at 6 months. Family history of Fabry was negative. His mRS had improved from 3 at baseline to 1 at 6 months. In summary, we found only 1 patient with a possible Fabry disease associated with the p.R118C variant, but none with a definitive diagnosis, corresponding to a prevalence of 1 of 395 (0.3%; 95% CI, 0.0–1.4) in our cohort.

### Outcome Measures

The mean duration of hospital stay was 9.6±18.4 days (10.3±19.1 days for IS and 1.7±2.4 days for TIA patients; P<0.001). The mean follow-up was 178.0±27.0 days (median, 178.0; interquartile range, 168–189). During that period, 14 recurrent ischemic events were documented in 13 of 379 patients (3.4%; Figure 1). These included 5 recurrent IS and 1 TIA in 6 of 349 patients (1.7%) who presented with IS, and 8 recurrent TIA in 7 of 30 (23.3%) patients who

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### Table 1. Baseline Demographics, Clinical Features, and Investigation (Proportions Unless Otherwise Indicated)

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort (n=397)</th>
<th>Age &lt;45 (n=213)</th>
<th>Age ≥45 (n=184)</th>
<th>P Value Between Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
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<tr>
<td>Women</td>
<td>179/397 (45.1%)</td>
<td>97/213 (45.5%)</td>
<td>82/184 (44.6%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Living at home</td>
<td>391/397 (98.5%)</td>
<td>210/213 (98.6%)</td>
<td>181/184 (98.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Living alone</td>
<td>66/397 (16.6%)</td>
<td>29/213 (13.6%)</td>
<td>37/184 (20.1%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Worked before</td>
<td>317/396 (85.9%)</td>
<td>171/197 (82.6%)</td>
<td>146/172 (84.9%)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Modifiable vascular risk factors</strong></td>
<td></td>
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<tr>
<td>Arterial hypertension</td>
<td>69/397 (17.4%)</td>
<td>27/213 (12.7%)</td>
<td>42/184 (22.8%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16/397 (4.0%)</td>
<td>3/213 (1.4%)</td>
<td>13/184 (7.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>70/397 (17.6%)</td>
<td>23/213 (10.8%)</td>
<td>47/184 (25.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>90/397 (22.7%)</td>
<td>43/213 (20.2%)</td>
<td>47/184 (25.5%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Smoking (ever)</td>
<td>197/397 (49.6%)</td>
<td>97/213 (45.5%)</td>
<td>100/184 (54.4%)</td>
<td>0.01</td>
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<td>Alcohol Abuse</td>
<td>42/397 (10.6%)</td>
<td>15/213 (7.0%)</td>
<td>27/184 (14.7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Body mass index (mean; kg/m²)</td>
<td>26.92±5.84</td>
<td>26.78±6.61</td>
<td>27.08±4.89</td>
<td>0.61</td>
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<tr>
<td><strong>Medication before the qualifying event</strong></td>
<td></td>
<td></td>
<td></td>
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<td>Antiplatelets</td>
<td>48/397 (12.1%)</td>
<td>18/213 (8.5%)</td>
<td>30/184 (16.3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>2/397 (0.5%)</td>
<td>2/213 (0.9%)</td>
<td>0/184 (0.0%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>41/397 (10.3%)</td>
<td>13/213 (6.1%)</td>
<td>28/184 (15.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Statins</td>
<td>39/397 (9.8%)</td>
<td>15/213 (7.0%)</td>
<td>24/184 (13.0%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous cerebrovascular events</td>
<td>52/397 (13.1%)</td>
<td>22/213 (10.3%)</td>
<td>30/184 (16.3%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>365/397 (92.0%)</td>
<td>198/213 (93.0%)</td>
<td>167/184 (90.8%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Transient ischemic Attack</td>
<td>32/397 (8.1%)</td>
<td>15/213 (7.0%)</td>
<td>17/184 (9.2%)</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>Type of acute infarct (in IS patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>58/362 (16.0%)</td>
<td>39/196 (19.9%)</td>
<td>19/166 (11.4%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Nonlacunar</td>
<td>304/362 (84.0%)</td>
<td>157/196 (80.1%)</td>
<td>147/166 (88.6%)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Acute infarct location (in IS patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral hemispheres</td>
<td>251/363 (69.1%)</td>
<td>126/197 (64.0%)</td>
<td>125/166 (75.3%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Deep brain structures</td>
<td>112/363 (30.9%)</td>
<td>71/197 (36.0%)</td>
<td>41/166 (24.7%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Silent brain infarcts</td>
<td>60/389 (15%)</td>
<td>31/210 (14.8%)</td>
<td>29/179 (16.2%)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

IS indicates ischemic stroke.
presented with TIA. In our cohort, no patient died or had intracerebral hemorrhage.

Figure 2 shows functional outcome as measured with the mRS for patients who presented with IS. Within 7 days from the qualifying event, 258 of 365 IS patients (70.7%) had mRS scores of 0 to 2. This proportion reached 305 of 349 patients (87.4%) at 6 months. At both time points, mRS did not differ between age categories. In the univariate analysis, diabetes mellitus, NIHSS score, aphasia \((P=0.05)\), paresis, nonlacunar infarct type, and having a job before IS were factors associated with functional dependence (mRS score of >2) at 6 months post-IS. The multivariable analysis revealed that presence of diabetes mellitus (odds ratio, 7.6; 95% CI, 1.9–31.2) and higher stroke severity (odds ratio, 2.2; 95% CI, 1.5–3.3) predicted dependence at 6 months, after adjusting for confounders (Table 3). The C statistic indicated good predictability with a value of 0.85.

Six months post-event, 372 of 377 (98.7%) patients returned home, whereas 5 of 377 (1.3%) remained in a rehabilitation or in a long-term care facility. Only 184 of 317 (57%) workers returned to their previous job.

**Discussion**

Early recognition of Fabry disease is important in young patients with cryptogenic IS given therapeutic and genetic counseling implications. However, a systematic genetic screening is expensive and provided a low yield in our cohort.

In this cohort study comprising young patients with a cryptogenic stroke from across Canada, we found a good recovery (87% with an mRS score of 0–2) and low recurrence at 6 months. Overall, screening by gene sequencing identified 8 of 395 participants (2%) with possible Fabry. Of those, 6 patients were carriers of multiple \(\alpha\)-GAL-A variants that were considered as nonpathogenic after further specialized investigations. A seventh had a single disease-neutral variant (p.D313Y), which was previously associated with pseudodeficient \(\alpha\)-GAL-A activity and leukoaraiosis. The eighth patient had a single variant (p.R118C) classified as GVUS.

Clinically, no patients exhibited the classic early-onset phenotype of Fabry. The late-onset, attenuated form of Fabry is therefore rare among the Canadian demographic ≤55 years presenting with cryptogenic IS or TIA: a prevalence value
of 0.3% (95% CI, 0.0%–1.4%) being determined if pathogenicity of the p.R118C variant is eventually confirmed as per recently proposed diagnostic criteria and 0.0% (95% CI, 0.0–1.0) if not. The very low prevalence we found is consistent with most previous studies based on various designs (Table 4).17–27 Two smaller North American studies17,18 and most European studies19–24 identified Fabry in 0.0% to 1.0% of cryptogenic IS or diverse other cerebrovascular conditions. Only 3 European studies reported a prevalence >1.0% in cryptogenic IS. Rolfs et al25 did not specify \( \alpha \)-GAL-A variants they considered biologically significant in 28 of 721 (3.9%) stroke patients (mostly ischemic). A second study found the neutral p.D313Y (with leukoaraiosis) but no other genetic variants in 1 of 92 cryptogenic IS or TIA.26 The third study found 3 of 104 patients with the neutral variant p.D313Y and another with the GVUS p.R118C and reduced leukocyte \( \alpha \)-GAL-A activity, suggesting pathogenicity.27 Conversely, our patient with the same p.R118C mutation had normal lyso-Gb3 blood levels, which does not support pathogenicity.

The likely yield of systematic testing for Fabry disease is therefore limited in cryptogenic IS or TIA of the young, at least among North Americans. Because positive screens and GVUS were rare in our cohort, we could not identify any stroke predictors of Fabry. Conversely, recognizing neutral variants is also important to avoid misdiagnosis of Fabry and unnecessary treatments. Fabry diagnosis must be based on appropriate investigations following guidelines.8

Similar to previous studies, we found low IS severity (mean NIHSS score of 3.1) and low IS recurrence (1.4%) and mortality (0%) at 6 months in young patients with cryptogenic IS.26,29 Our study shows favorable functional outcome in this group (71% with mRS score of 0–2 at 7 days post-IS and 87% at 6 months), but 43% of previous workers are not returning to previous employment. This compares with other studies combining all IS causes, which reported mRS score of 0 to 2 in 70% of young IS survivors at hospital discharge and in 81% to 85% at 3 to 6 months, but only 24% of them working full time after 3 months.24,30,31 Between 50% and 70% of young IS patients, eventually return to work after a mean of 8 months, with 25% of workers needing task adjustment.2 Overall, mortality is lower in young IS patients compared with older patients, but is 10× that of the general population of the same young age,2 stressing the importance of secondary prevention.

Our study has some limitations. First, our cohort included patients with cryptogenic IS and TIA. Diagnosis of TIA is a challenge, especially in the young where potential mimickers are common (eg, migraine aura, anxiety, and epilepsy). Only

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**Figure 2.** Functional outcome (modified Rankin Scale [mRS]) ≤7 d and 6 mo post-ischemic stroke, for the entire group and by age category.

**Table 3. Predictors of Poor Outcome at 6 Months Post-Ischemic Stroke**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range (Third vs First Quartiles)</th>
<th>Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36–49</td>
<td>0.657 (0.392–1.100; 0.968 (0.931–1.007) per unit change</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>0–4</td>
<td>16.261 (4.524–58.450)</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs no)</td>
<td></td>
<td>7.602 (1.852–31.202)</td>
</tr>
<tr>
<td>Sex (woman vs man)</td>
<td></td>
<td>1.318 (0.626–2.774)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale.
those with speech or motor deficit were enrolled to minimize risk of misdiagnosis, and they accounted for only 8.1% of our cohort. Second, the diagnosis of cryptogenic cause also is difficult. The proportion of ischemic cerebrovascular events that remain unexplained depends on the investigation extent and timing and the etiologic classification scheme that is used. We used a well-defined protocol applying an accepted definition of cryptogenic stroke by having predetermined essential baseline investigations as inclusion criteria. Third, the diagnosis of Fabry was based on screening by \(\alpha\)-GAL-A gene sequencing and confirmation by measurement of lyso-Gb3 plasma levels. \(\alpha\)-GAL-A activity measurement is recommended for Fabry screening in male (but not in female) because it is sensitive, reliable, rapid, and cost-effective, with genetic analysis being used in positive screenings (and as first-step investigation in female)." Because storage and shipping may alter \(\alpha\)-GAL-A activity and cause false-positive screenings, our multicenter study primarily investigated both sexes with gene sequencing. As this approach detects \(>97\%\) of pathogenic mutations or GVUS, underestimation of Fabry prevalence is possible, but probably minimal. Because \(\alpha\)-GAL-A activity was not measured, distinction between nonclassical Fabry and neutral variant following recent guidelines was not possible, at least in our p.R118C male patient. Finally, some well-established predictors of outcome (eg, thrombolysis and thrombectomy) were unavailable from our database and could not be integrated in our multivariable models of functional outcome.

Despite these limitations, the main strength of our study is the substantial number of young patients we recruited, exclusively with cryptogenic IS or TIA. The size of our cohort is larger than the sum of 3 previous Fabry studies targeting cryptogenic events, resulting in a more precise prevalence estimate. Our study provides some insight on the overall prognosis of young patients with a cryptogenic IS, which accounts for one third of cases. Finally, validity of our study cohort is supported by excellent population coverage (93.2%) and nearly-complete follow-up data. All mRS scores were available at \(\leq7\) days and 95.5% (379/397) at 6 months.

**Conclusions**

Our study shows a low prevalence of Fabry in young Canadians with cryptogenic IS or TIA. This finding suggests limited clinical use of systematic Fabry screening by gene sequencing in this group. Fabry screening should be done following guidelines and possibly limited to those with disease markers (eg, kidney and cardiac disease). Cryptogenic IS patients had mild events and favorable outcomes (mRS score of <2, low incidence of recurrent IS, and mortality) at 6 months. Working capacity limitations and other socioeconomic consequences are nevertheless common among young patients with cryptogenic IS and likely substantially contribute to important societal costs in this patient demographic. This argues for continued effort to better etiologically define and prevent cryptogenic IS in the young.

**Appendix**

The CFSSI Investigators are Sylvain Lanthier, Gustavo Saposnik, Gerald Lebovic, Karen Pope, Dan Selchen, David F. Moore, Jean-Martin Boulanger, Brian Buck, Ken Butcher, Martin del Campo, Sylvie Gosselin, Vladimir Hachinski, Michael D. Hill, Ariane Mackey, Manu Mehdirdita, J. David Spence, Grant Stotts, Rick Swartz, Michael L. West, and Chidam Yegappan.

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Disclosures

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References


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