Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events
Natural History Data From the Fabry Registry

Katherine Sims, MD; Juan Politei, MD; Maryam Banikazemi, MD; Philip Lee, FRCP

Background and Purpose—Stroke is a common and serious clinical manifestation of Fabry disease, an X-linked lysosomal storage disorder caused by deficiency of α-galactosidase A activity. This study was undertaken to better understand the natural history of cerebrovascular manifestations of Fabry disease.

Methods—Data from 2446 patients in the Fabry Registry were analyzed to identify clinical characteristics of patients experiencing stroke during the natural history period (ie, before enzyme replacement therapy).

Results—A total of 138 patients (86 of 1243 males [6.9%] and 52 of 1203 females [4.3%]) experienced strokes. Median age at first stroke was 39.0 years in males and 45.7 years in females. Most patients (70.9% of males and 76.9% of females) had not experienced renal or cardiac events before their first stroke. Fifty percent of males and 38.3% of females experienced their first stroke before being diagnosed with Fabry disease. Thirty patients (21 males and 9 females) had strokes at age <30 years. Most patients (86.8%) had ischemic strokes, but 16.9% of males and 6.9% of females had hemorrhagic strokes, among those for whom stroke type was reported. At the most recently available follow-up examination after their first stroke, 60% of males and 25.5% of females exhibited stage 3 to 5 chronic kidney disease and 66.1% of males and 59.5% of females had left ventricular hypertrophy.

Conclusions—All patients with Fabry disease, regardless of age or gender, should be monitored for possible cerebrovascular complications, as stroke can occur in the absence of other key signs of the disease. (Stroke. 2009;40:788-794.)

Key Words: Fabry disease □ cerebrovascular accident □ stroke □ registries

Fabry disease is an X-linked lysosomal storage disorder, characterized by decreased or absent activity of lysosomal α-galactosidase A.1 As a result, globotriaosylceramide (GL-3) and other glycosphingolipids progressively accumulate within many cell types, including the vascular endothelium.1 Early symptoms of Fabry disease (typically beginning during childhood) include neuropathic pain, gastrointestinal dysfunction, and hypohidrosis.2,3 Later, vital organ function progressively declines, putting older patients at risk of developing renal failure, cardiovascular dysfunction, and stroke.2,3

Enzyme replacement therapy (ERT) with recombinant human α-galactosidase A effectively reduces plasma and tissue GL-3 accumulation4-6 and attenuates many signs and symptoms of Fabry disease.4-9 With close monitoring, the renal and cardiac manifestations of Fabry disease can be detected and appropriate treatment initiated before the onset of end organ failure.8,9

Although patients with Fabry disease are known to experience transient ischemic attacks (TIAs) and strokes at an early age,2,3 there are few quantitative markers of disease burden in the central nervous system. Fabry patients frequently exhibit white matter lesions, which can be detected by conventional neuroimaging methods (reviewed in9). Recently, magnetic resonance diffusion tensor imaging has been used to quantify these abnormalities.11 However, the risk of clinical cerebrovascular manifestations, such as stroke and TIAs, is difficult to predict.

Several studies have estimated the incidence of stroke in various small cohorts of patients with Fabry disease. Vedder et al12 reported that 12 of 25 males (48%) and 3 of 41 females (7%) had experienced cerebrovascular accidents or lacunar stroke, at a median age of 46 and 52 years, respectively. Gupta et al13 reported that 4 of 54 female Fabry patients (7%) had experienced strokes, at a median age of 51 years. Mehta et al14 reported that 24 of 216 males (11%) and 27 of 172 females (16%) had experienced either a TIA or a stroke. Grewal reviewed various types of imaging data and reported that 8 of 33 Fabry patients (24%) had experienced strokes at a median age of 26.5 years.15 Because of the various ways these and other studies defined cerebrovascular complications, the stroke incidence and median age at first stroke cannot be readily compared across studies.
A screening study of 721 young patients (age 18 to 55) who had strokes of unknown etiology reported that 4.9% of males and 2.4% of females had Fabry disease. Based on these findings, it was estimated that 1% to 2% of all stroke patients within this age range could have Fabry disease. Others have suggested that this percentage may be higher or lower.

The mechanisms underlying stroke pathogenesis in Fabry disease have not been clearly delineated. Progressive accumulation of GL-3 within the endothelium of intracranial blood vessels is thought to play a primary role in the vasculopathy and risk of ischemic stroke. However, secondary factors, including abnormalities in cerebral blood flow velocity, a prothrombotic state, and increased production of reactive oxygen species have also been identified as contributing to the development of stroke in Fabry disease.

A better understanding of the natural history of cerebrovascular manifestations of Fabry disease may provide valuable information about which patients may be at greatest risk for stroke. Such information can also raise awareness of Fabry disease among the broader medical community and highlight the importance of improved monitoring and management options.

**Data Analysis and Statistics**

The Fabry Registry is an ongoing, observational database that compiles clinical and laboratory data on patients with Fabry disease. The Fabry Registry began enrolling patients and collecting data in April 2001. As of October 5, 2007, the Fabry Registry included 2446 patients with known ERT status. All patients with Fabry disease are eligible for enrollment, regardless of age, gender, symptoms, or whether they are receiving ERT. Patient and physician participation is voluntary. All patients provide informed consent through local Institutional Review Boards/Ethics Committees and may decline to participate or withdraw consent at any time. Treating physicians determine the actual frequency of assessments according to patients’ individualized needs. A schedule of recommended clinical assessments is available at http://www.fabryregistry.com. Given the voluntary nature of reporting data, patients’ ages at clinical assessments and time intervals between assessments are variable.

Data were analyzed using SAS statistical software version 8 (SAS Institute Inc) and summarized using descriptive statistics. A Wilcoxon signed rank test was used to compare median age at symptom onset and median age at diagnosis among patients who had strokes versus patients who did not.

Data from untreated Fabry Registry patients as well as data obtained before initiation of treatment from ERT-treated patients were included in these analyses. The period of data extended from date of birth until last available follow-up record for each patient. Patients for whom ERT status was unknown (1.8% of all patients enrolled) were excluded from these analyses, to ensure all stroke events occurred before initiation of ERT.

**Definition of Stroke and Cardiovascular and Renal Events**

Strokes were defined as either ischemic or hemorrhagic cerebrovascular accidents. At the time of patient enrollment, participating physicians were asked to indicate whether patients had a previous medical history of stroke and to report any subsequent strokes to the Fabry Registry. If patients experienced a stroke while participating in the Fabry Registry, physicians were asked to provide clinical details, including the type of stroke, the location of the stroke, what type of brain imaging was performed and any findings from brain imaging. Cardiovascular events were defined as myocardial infarction, significant cardiac procedures (eg, pacemaker placement, bypass, stent placement, valve replacement, transplantation), arrhythmia, angina pectoris, or congestive heart failure. Renal events were defined as renal dialysis or renal transplantation.

**Analysis of Risk Factors**

Medical history data in the Fabry Registry were analyzed to determine how many patients ever reported experiencing a TIA, cardiac arrhythmia, hypertension, diabetes, migraine, headache/migraine, abnormal cholesterol levels, or a history of smoking. These risk factors may have occurred either before or after a patient’s first stroke, up until October 5, 2007.

**Results**

As of October 5, 2007, 138 of 2446 Fabry Registry patients had experienced stroke during the natural history period, including 86 of 1243 males (6.9%) and 52 of 1203 females (4.3%). Most patients (115 of 138, 83.5%) had been enrolled in the Fabry Registry for ≥2 years. The mean follow-up period among this cohort (from birth to last follow-up visit) was 40 ± 11.9 years among males (n = 86) and 46 ± 14.8 years among females (n = 52). Demographic data are summarized in Table 1.

The median age at first stroke was 39.0 years in males and 45.7 years in females (Table 1). Interestingly, patients who had strokes reported the onset of Fabry symptoms at a later age than those who did not, among both genders. Males who had a stroke experienced their first symptoms at a median age of 11.1 years, versus 9.6 years among males who did not have strokes (P < 0.02). Females who had strokes experienced first symptoms at a median age of 24.0 years, versus 14.6 years for females who did not have strokes (P < 0.06). Similarly, Fabry Registry patients with strokes were diagnosed later than patients who did not (Table 1).

As shown in Figure 1, most patients experienced their first stroke between 20 and 50 years. Males generally experienced their first stroke at an earlier age than females. The small percentage of males experiencing their first stroke at ≥60 years (2 of 86 patients, or 2.3%) reflects the small number of surviving males in this age category. Only 32 of 1243 males in the Fabry Registry (2.6%) were ≥60 years old, compared to 133 of 1203 females (11.1%). Thirty of 138 stroke patients (21.7%) had strokes at <30 years, including 2 patients who had strokes during their teen years (a 13.8 year-old male and a 19.8 year-old female). Among those who had strokes at <30 years, the median age was 25.8 years in males (n = 21) and 24.1 years in females (n = 9).

The incidence rates of first strokes in all 2446 Fabry Registry patients in the natural history population and in the general US population are shown in Figure 2. Within each age category, Fabry patients exhibited a markedly higher incidence of stroke than the general US population. Among Fabry males >45 years, stroke incidence increased dramatically with each passing decade. The mean age at first stroke among Fabry patients (39.8 years for males and 45.7 years for females, Table 1) was also considerably younger than the mean age at first stroke among the general population: 76 years in males and 81 years in females, for strokes occurring between 1990 and 2004.24

The majority of first strokes experienced by Fabry Registry patients were described as ischemic. Of the 121 patients for
whom stroke type was reported, 105 (86.8%) had ischemic
and 16 had hemorrhagic strokes (13.2%). Hemorrhagic
strokes were more prevalent in males (13 of 77, 16.9%) than
in females (3 of 44, 6.8%). Of the 16 patients with hemor-
rhagic strokes, the median age at first stroke was 47.8 years
in males (range 25.8 to 57.3) and 57.7 years in females (range
32.6 to 65). For ischemic strokes in which vessel size was
reported, the majority (38 of 54, 70.4%) occurred within
small vessels (lacunar). Where reported, the most common
areas where ischemic strokes occurred were the middle
cerebral artery territory (15 of 38, 39.5%), the anterior
cerebrum (10 of 38, 26.3%), and vertebrobasilar region (7 of
38, 18.4%). For ischemic strokes, the vessel size and location
of strokes were similar in males and females.

Of the 138 patients who had strokes, 93 patients (67.4%)
also reported experiencing a cardiac or renal event at some
time. The majority (70.9% of males and 76.9% of females)
either had a stroke before a renal or cardiac event or
experienced a stroke only (ie, did not have any other clinical
events), as shown in Figure 3. Females were much more
likely than males to experience a stroke as their only clinical
event (26 of 52, 50.0%), compared to males (19 of 86,
22.1%). Furthermore, 18 of 47 (the temporal relationship
between stroke and diagnosis was unknown for 5 of the 52
females) females (38.3%) and 43 of 86 males (50.0%)
experienced their first stroke before they were diagnosed with
Fabry disease. Thus, most patients had either not experienced
other major complications or were not known to have Fabry
disease before their stroke.

We also examined the sequence of clinical events among
the 30 patients who had strokes at a young age and the 16
patients who had hemorrhagic strokes (Figure 3). Patients

Table 1. Summary of Demographics of Fabry Registry Patients by Stroke Category and by Gender

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Males With Strokes (n=86)</th>
<th>Males Without Strokes (n=1157)</th>
<th>Females With Strokes (n=52)</th>
<th>Females Without Strokes (n=1151)</th>
<th>All Patients With Strokes (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80 (93.0)</td>
<td>867 (74.9)</td>
<td>46 (88.5)</td>
<td>892 (77.5)</td>
<td>126 (91.3)</td>
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<tr>
<td>Black</td>
<td>1 (1.2)</td>
<td>25 (2.2)</td>
<td>2 (3.8)</td>
<td>19 (1.7)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (2.3)</td>
<td>82 (7.1)</td>
<td>2 (3.8)</td>
<td>76 (6.6)</td>
<td>4 (2.9)</td>
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<tr>
<td>Asian</td>
<td>0</td>
<td>42 (3.6)</td>
<td>0</td>
<td>12 (1.0)</td>
<td>0</td>
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<tr>
<td>Other</td>
<td>2 (2.3)</td>
<td>42 (3.6)</td>
<td>1 (1.9)</td>
<td>28 (2.4)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Not Specified</td>
<td>1 (1.2)</td>
<td>99 (8.6)</td>
<td>1 (1.9)</td>
<td>124 (10.8)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Age at First Stroke (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39.8 (11.92)</td>
<td>45.7 (14.75)</td>
<td>42.0 (13.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>39.0 (13.8, 80.1)</td>
<td>45.7 (19.8, 74.8)</td>
<td>40.6 (13.8, 80.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Fabry Symptom Onset (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>70</td>
<td>885</td>
<td>43</td>
<td>618</td>
<td>113</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>16.3 (13.15)</td>
<td>13.8 (12.14)</td>
<td>26.6 (18.99)</td>
<td>20.3 (15.41)</td>
<td>20.2 (16.34)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>11.1 (3.8, 63.4)</td>
<td>9.6 (0.0, 70.6)</td>
<td>24.0 (4.6, 69)</td>
<td>14.6 (0.0, 77.7)</td>
<td>12.3 (3.8, 69)</td>
</tr>
<tr>
<td>Age at Fabry Diagnosis (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>86</td>
<td>1139</td>
<td>47</td>
<td>1103</td>
<td>133</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>35.8 (16.01)</td>
<td>26.2 (15.73)</td>
<td>40.4 (18.54)</td>
<td>32.6 (17.62)</td>
<td>37.4 (17.03)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>35.5 (4.3, 78.9)</td>
<td>24.0 (0.0, 81)</td>
<td>38.1 (0.0, 78.3)</td>
<td>32.0 (0.0, 80.6)</td>
<td>36.5 (0.0, 78.9)</td>
</tr>
</tbody>
</table>

Stroke patients are those with recorded stroke events during the natural history time period, i.e., before the start of ERT. Note that dates of symptom onset and diagnosis were not available for all patients. SD indicates standard deviation.

Figure 1. Age at first stroke in Fabry Registry patients. Percentages of patients experiencing their first stroke during 6 age categories are shown. Data for males are in dark gray bars and data for females are in light gray bars, with the number of patients in each age category shown above each bar. All data are from patients not treated with ERT at the time of their first stroke.
who had strokes at <30 years, particularly females, were more likely than patients in the overall stroke population to have experienced a stroke as their only clinical event (9 of 21 males, 42.9% and 6 of 9 females, 66.7%). Of these 30 young patients, only 1 male and 1 female had experienced a renal or cardiac event before their stroke. Among the 16 patients who had hemorrhagic strokes, 6 of 13 males (46.2%) had experienced a renal or cardiac event before their stroke. The 3 females who had hemorrhagic strokes each experienced their first stroke as their only clinical event.

Patients’ renal and cardiac characteristics at the most recently available follow-up examination after their first stroke were also analyzed, as summarized in Table 2. Of those for whom renal data were available, 49 of 82 males (59.8%) and 12 of 47 females (25.5%) exhibited stage 3 to 5 chronic kidney disease. Of the 93 patients with echocardiographic data, 37 of 56 males (66.1%) and 22 of 37 females (59.5%) had left ventricular hypertrophy.

Not surprisingly, patients who had strokes were much more likely to have reported a medical history of various risk factors for strokes, as compared to other patients in the Fabry Registry. Compared to nonstroke patients, those who had strokes were more likely to report TIsAs (36.2% versus 5.4%), arrhythmias (32.6% versus 12.7%), or hypertension (52.9% versus 20.5%). As shown in Figure 4, similar percentages of male and female stroke patients reported a history of TIsAs. Male stroke patients were more likely than females to have reported a history of arrhythmias. A greater percentage of females who had strokes reported a history of hypertension (32 of 52, 61.5%), as compared to males (41 of 86, 47.7%).

Among the subpopulations of patients with strokes at <30 years (all of whom had ischemic strokes) and those with hemorrhagic strokes, the proportion of patients with a history of TIsAs or arrhythmias was generally similar to that observed in the overall population of Fabry stroke patients (data not shown). Patients with hemorrhagic strokes were more likely to have reported a history of hypertension (11 of 16, 68.9%) than patients with a stroke <30 years (8 of 30, 26.7%). Overall, 73 of 138 stroke patients (52.9%) had a history of hypertension.

**Discussion**

The Fabry Registry has collected clinical data from 2446 Fabry patients. This large, international cohort provides a...
These analyses evaluated data from 138 patients who experienced strokes before ERT. The mean age at first stroke for Fabry patients was considerably younger than that of the general U.S. population. As in the general population,25,26 the incidence of stroke increased with increasing age in Fabry Registry patients. The incidence of stroke during each decade was markedly higher among Fabry patients, compared to the general population. Although it is well known that Fabry patients have a high risk of stroke,1–3,27 this is the first study to systematically analyze the rates of stroke events in a large Fabry population and to evaluate the clinical characteristics of these stroke patients.

The fact that 4.3% of the females in the Fabry Registry had experienced a stroke supports the growing body of evidence that heterozygous females develop substantial symptoms and signs of Fabry disease and are at risk of premature death.3,13 Males experienced first strokes at an earlier age than females (median age 39.0 years versus 45.7 years, respectively), which is consistent with males typically exhibiting more severe and earlier signs and symptoms of Fabry disease.3,13 However, 17% of females who had strokes experienced their first stroke before 30 years, including 1 female at age 19.8 years.

Sixty-one of the 133 stroke patients (45.9%) for whom data were available experienced their first stroke before being diagnosed with Fabry disease. In these 61 patients, the median time from first stroke to diagnosis was 4.8 years (data not shown). This highlights the need for greater awareness and earlier diagnosis, before the major clinical manifestations of Fabry disease occur. Most patients, particularly females and patients <30 years, either had their first stroke before any renal or cardiac events or did not have any other clinical antiplatelet or anticoagulation prophylactic treatment. Evaluation of comorbid prothrombotic risk factors may also identify those with higher thromboembolic stroke risk.

Figure 4. Medical history of various risk factors in Fabry Registry stroke patients. Bar graphs indicate relative percentages of males and females with strokes who also reported a history of TIA, arrhythmias, or hypertension at the time they enrolled in the Fabry Registry, as indicated. Black bars indicate patients with strokes who also reported these risk factors, dark gray bars indicate patients with stroke who did not report these risk factors, and light gray bars indicate patients who had not reported this information or for whom this information was unknown. Data are expressed as relative percentages, with the number of patients in each group indicated above each bar. Note that these risk factors may have occurred either before or after a patient’s first stroke.
events. Thus, many Fabry patients may not exhibit obvious major signs of the disease before a stroke occurs.

Where stroke type was reported, 86.8% of first strokes were ischemic and 13.9% were hemorrhagic. This proportion is similar to that observed in the general population of stroke patients, though hemorrhagic strokes were more common in Fabry males (16.9%) than in females (6.8%). Glycolipid deposition within intracerebral blood vessels would be predicted to put patients at risk for ischemic stroke, but the finding that 16 patients had hemorrhagic strokes was somewhat unexpected. Vertebrobasilar dolichoectasia, which is primarily associated with ischemic strokes, has also been linked with hemorrhagic strokes, particularly in patients with hypertension. Dolichoectasia of the basilar artery has been reported in Fabry disease. Though hypertension was more prevalent in the subset of patients with hemorrhagic strokes, none of these patients exhibited hemorrhage within the vertebrobasilar region.

Various risk factors were identified among Fabry stroke patients. The 3 risk factors most strongly associated with stroke were a history of TIAs, arrhythmias, or hypertension. Similar proportions of males and females reported a history of TIAs, whereas arrhythmia was more prevalent in male stroke patients and hypertension was more strongly associated with stroke in females. Thus, Fabry patients who experience TIAs, hypertension, or arrhythmia are at risk of stroke, and management should be proactive and specifically targeted in those who experience these premonitory events. However, patients who do not exhibit these signs may still be at risk of stroke, as many patients who experienced a stroke did not report any of these risk factors. Although it has not been demonstrated that ERT can prevent strokes, it has been shown to ameliorate many of the major signs and symptoms of Fabry disease, and patients at risk of stroke should also be considered for treatment with ERT.

The precise pathological mechanisms underlying strokes in patients with Fabry disease are uncertain, though various abnormalities in cerebral blood flow and in intracranial vessel walls have been identified (reviewed in ). In addition, characteristic white matter lesions are very common in patients with Fabry disease, and the prevalence of white matter lesions among these patients grows with increasing age (reviewed in ). As mentioned, Fabry patients can have dolichoectasia of the basilar artery. Finally, microvascular cerebral abnormalities were detected in 2 male Fabry patients during childhood (ages 8 and 11 years), when they showed no clinical evidence of renal or cardiac disease. In future studies, detailed analyses of cerebral MRI data may provide valuable information for predicting which patients are at high risk for strokes.

The finding that nearly half of these patients experienced their first stroke before diagnosis is contrary to the conventional view of the “classical” progression of Fabry disease, namely that early symptoms (ie, hypohidrosis, neuropathic pain, and gastrointestinal dysfunction) begin in childhood and that major end-organ events (ie, renal dysfunction or cardiovascular disease preceding stroke) occur during the fourth or fifth decades of life. Although many patients do exhibit the classical type of gradual disease progression, it is possible at least some who have strokes experience less severe “early symptoms” of the disease, and therefore go undiagnosed until they have a stroke. Indeed, patients who had strokes, particularly females, reported experiencing symptoms at an older age than Fabry Registry patients without strokes. Accordingly, patients with strokes were also diagnosed at a much later age. Furthermore, many patients with cryptogenic strokes (4.9% of males and 2.4% of females) were found to have undiagnosed Fabry disease. Because most Fabry Registry patients did not report other major clinical signs before their first stroke (ie, cardiovascular or renal dysfunction), physicians must be vigilant for cerebrovascular risk factors and complications in all Fabry patients, even those who do not exhibit substantial cardiovascular or renal disease.

It is imperative that Fabry patients are diagnosed as early as possible, particularly given the possibility of this relatively “silent progression” to stroke. All patients should be closely followed and evaluated to monitor the progression of Fabry disease, and patients who experience TIAs, arrhythmia, or hypertension should be considered at risk of stroke and management and therapy adjusted accordingly.

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Disclosures

None.

References


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