Prevalence of Fabry Disease in Stroke Patients—A Systematic Review and Meta-analysis

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Background: Fabry disease is an uncommon but treatable cause of stroke. Enzyme replacement therapy helps improve neurologic symptoms. We conducted a systematic review and meta-analysis to evaluate the prevalence of Fabry disease in stroke patients. *Methods:* We searched MEDLINE and EMBASE databases for relevant articles published in English up to February 2013. Studies that reported incidence or prevalence of Fabry disease in stroke patients were included. Two reviewers independently assessed studies to determine eligibility, validity, and quality. Meta-analysis was performed to calculate the prevalence of Fabry disease by etiology and gender. *Results:* Nine studies (n = 8302 patients) met the inclusion criteria. Eight studies (n = 8148) examined the prevalence of Fabry disease in young stroke patients. Overall qualities of included studies were moderate to high. The prevalence of Fabry disease ranged from .4% to 2.6% on strokes of any etiologies. In cryptogenic stroke, the prevalence ranged from .6% to 11.1%, 4.5% in men (95% confidence interval [CI] = 3.2%-6.3%) and 3.4% in women (95% CI = 1.0%-10.7%). The prevalence of Fabry disease in patients with all etiologies was similar in men (.9% [95% CI = .3%-2.3%]) and (1.4% [95% CI = .7%-2.7%]) in women. *Conclusions:* Fabry disease may explain approximately 1% of all strokes in the young, including 3%–5% of cryptogenic strokes. The confirmation of Fabry disease may be challenging as there are different criteria for men and women. Early recognition of Fabry disease may help initiate the appropriate treatment to decrease the risk of subsequent complications. **Key Words:** Fabry disease—stroke—youth—prevalence—meta-analysis.

Introduction

Fabry disease is an X-linked lysosomal storage disorder characterized by glycosphingolipid accumulation because of lysosomal α-galactosidase A deficiency.[1,2] The most common organs and tissues affected by Fabry disease include the kidney, myocardium, and brain. The impairments of arteries lead to renal insufficiency, left ventricular hypertrophy, arterial ectasia, atherosclerosis,

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Received June 26, 2013; revision received August 6, 2013; accepted August 14, 2013.

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Disclosures: Q.S. and J.P. have received educational grant from Shire Human Genetic Therapies (EG-CAN-000231) to conduct the literature review and the analysis. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. Shire had no direct involvement or input in the study or manuscript. The final decision to submit the manuscript was from the authors.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.08.010

and stroke.[3-6] Organ functional deterioration often presents in fourth or fifth decade of life, which is earlier than general population.[7-9] As a result, Fabry disease is one of the under-recognized causes of premature and advanced atherosclerotic disease, besides hypertension, smoking, familiar dyslipidemia, and hyperhomocysteinemia. Both men and women can be similarly affected by this disorder with manifestations from remaining asymptomatic to irreversible organ failure. However, women are generally having late symptoms than men.[10]

Typical clinical manifestations such as angiokeratoma, anhidrosis, and acroparesthesias can be absent in young adults, making the diagnosis of Fabry disease a challenge to clinicians. A recent systematic review studied prevalence of Fabry disease in high-risk populations, focusing on patients with dialysis, renal transplantation, hypertrophic cardiomyopathy, and stroke.[11] However, only 2 studies were related to stroke patients.[5,12] In the past 2 years, quite a few studies[13-19] have been conducted on the prevalence of Fabry disease in stroke patients. To date, no meta-analysis has been conducted to determine the incident risk of Fabry disease in patients with cryptogenic stroke. In the present study, we conducted a systematic review and meta-analysis to determine the prevalence and clinical manifestations of Fabry disease in stroke patients.

Materials and Methods

Search Sources and Searches

Two reviewers (Q.S. and J.C.) conducted a literature search of MEDLINE and EMBASE in February 2013. Computer searches based on key words were conducted. References from previously retrieved articles were also searched. We generated search terms with the assistance of a research librarian. Details of the search strategy can be found in the Supplementary Appendix 1.

Study Selection

Research articles reporting incidence or prevalence of Fabry disease were included for review if they met the following inclusion criteria: (1) the study was designed as a prospective, retrospective cohort study or cross-sectional study, (2) the incidence or prevalence of Fabry disease was reported in study, (3) the study population had episode of stroke, regardless of type (ie, ischemic versus hemorrhagic, first ever versus recurrent, etc.), and (4) the study was written in English. Figure 1 shows a flow chart of the search.

Data Extraction and Quality Assessment

Data were extracted to a form that included following information: first author, year of publication, study population characteristics, screening and confirmatory tests, and prevalence of Fabry disease.

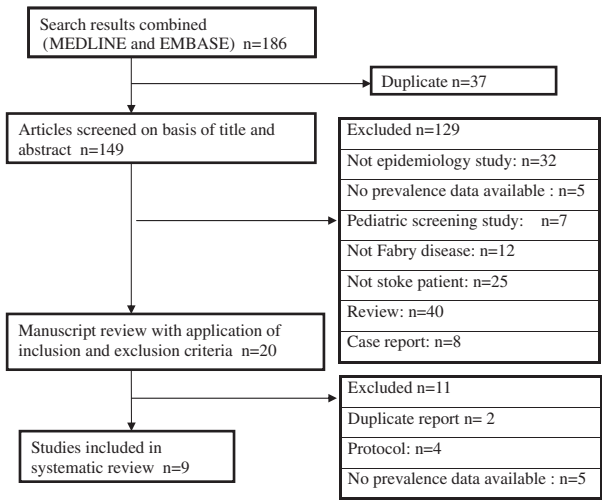

Figure 1. *Schema of systematic review.*

As there is no widely acceptable quality appraisal tool for prevalence studies, we developed an assessment tool (Supplementary Appendix 2) for this purpose. It comprises 6 items addressing the study quality of participant sampling (2 items: inclusion criteria of the study, sampling strategy) and diagnostic procedure derived from literature (4 items: diagnostic criteria, blindness, internal reliability, and attrition).[20,21] Each question was answered "yes," "no," or "unclear." One point per item would be assigned if answer was "yes" except diagnostic decision that has maximal 2 points. The maximal summary score of this scale is 7. We considered study with scoring 3 or lower as low quality, whereas 4 or above as moderate to high quality.

Two reviewers (Q.S. and J.C.) independently assessed the eligibility of the study and conducted data extraction and quality appraisal. Third reviewer (G.S.) was consulted if disagreement remained.

Data Synthesis

Statistical analysis was performed using Comprehensive Meta-analysis software. The prevalence of Fabry disease was determined and reported by stroke etiology (all stroke versus cryptogenic stroke) and by gender. For women, *α-GAL* gene mutation was considered diagnosis of Fabry disease. For men, either decreased α-galactosidase activity or *α-GAL* gene mutation was considered a diagnosis criterion.[10]

Studies were compared for heterogeneity using the chi-square statistic (P value $< .05$ considered statistically significant) and an I^2 test ($I^2 > 50\%$ considered substantial heterogeneity[22]). A fixed-effects model was initially used in this review. A random-effects model was applied if heterogeneity existed. We conducted a priori hypothesis to explain the heterogeneity that might exist between the studies. The potential sources were stroke etiology, demographic difference in populations, time of assessment, and