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IRB Proposal
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Rate of silent brain infarcts in young adults with type I diabetes

1. Study Purpose and Rationale.

Stroke is often considered a disease of the old. However, stroke in young adults is well described and is sometimes devastating, leaving functional young people unable to work and with poor quality of life. Recent studies reveal that the causes of ischemic stroke in young adults are similar to those in older adults and include atherosclerosis, small vessel disease, and cardiac emboli (Larrue et al., 2011; Putaala et al., 2009). However, several special populations have been shown to have an increased risk of stroke as young adults. These populations include patients with antiphospholipid syndrome, Fabry syndrome, and type I diabetes—the focus of this proposed study.

Subclinical cerebrovascular disease can result in silent brain infarcts (SBI), defined as cerebral infarcts (usually greater than 3mm) evident on imaging such as CT or MRI that have no associated clinical stroke episode (Zhu et al., 2011). The exact technical definition of SBI has varied among studies, resulting in a range of SBI from 8-28 percent for community-dwelling older adults who have never had a stroke (for review see Vermeer et al., 2007). Of eight major studies examining SBI in the general population of elderly adults, the median rate was 12.5 percent, with studies with higher mean age reporting higher rates of SBI (Vermeer et al., 2007). Few high-quality studies exist to define the rate of SBI in healthy younger adults, though the rate is not clearly known to exceed 10% for patients 40-60 years old and has been lower for those under 40 years of age (Vermeer et al., 2007).

Evidence from older adults indicates that SBI are not merely incidental MRI findings, but rather useful prognostic indicators both in stroke patients and individuals who have never had a stroke. In older adults who have already had a stroke, the presence of SBI at the time of stroke diagnosis has been associated with increased risk of recurrent stroke in patients with atrial fibrillation (EAFT Study Group, 1996). Perhaps more importantly, the presence of one or more SBI in community-dwelling older adults who have never had a stroke has been shown to increase the likelihood of a future stroke by two to four times compared to individuals without SBI (Bernick et al., 2001; Vermeer et al., 2003b).

A single study has evaluated the presence of SBI in young adult stroke patients (Putaala et al., 2011). In that study, 669 patients who had suffered a first ischemic stroke at ages 15 to 49 underwent MRI as part of routine clinical care. The MRI findings revealed that 13 percent of the patients had evidence of SBI in addition to the lesion that corresponded to their clinical stroke. The authors did not report which comorbid conditions or demographic factors were associated with SBI. Recurrent stroke was significantly higher in patients with SBI than without SBI. Of note, the group most likely to have a recurrent

stroke was patients with type I diabetes. It would have been very valuable to have known the percentage of patients with type I diabetes who had SBI.

Relatively few studies have examined stroke in type I diabetes. Using data from the Nurses Health Study (N>100,000), researchers revealed that patients aged 30-55 years of age with type I diabetes were four times more likely to have an ischemic stroke than age-matched non-diabetic individuals (Janghorbani et al., 2007). No previous studies have specifically examined SBI in patients with type I diabetes. Studies have examined the association of type II diabetes and SBI with mixed results. Two studies in a general elderly population have studies have found a positive association between type II diabetes and SBI (Kohara et al., 2003; Vermeer et al., 2003a). Several other studies have found no significant association between type II diabetes and SBI (Vermeer et al., 2007). Five studies have examined SBI in elderly type II diabetics. Vermeer et al. (2007) pooled the data from these five studies and revealed a mean rate of SBI of 38% in type II diabetics (Shinoda-Tagawa et al., 2002; Eguchi et al., 2003; Nakamura et al., 2005; Kawamura et al., 2006; Manschot et al., 2006).

The study proposed here aims to establish the rate of SBI in very young adults aged 25 to 40 years old who have had type I diabetes for at least ten years and who have never had a stroke or transient ischemic attack (TIA). The alternative hypothesis is that in these very young adults who have a longstanding cause of small vessel disease, the rate of SBI will be much higher than in non-diabetic young adults and will be similar to that of older adults with risk factors for small vessel disease, namely type II diabetes. The published mean rate of SBI in older adults with type II diabetes is 38% (Vermeer et al., 2007). Therefore, the present study will be powered for an estimated rate of 38% SBI. However, the findings are likely to be of clinical interest even if the rate is as low as 12.5%, consistent with the median rate in eight large studies of elderly adults and substantially higher than the published rate in healthy younger adults (Vermeer et al., 2007).

Given that the rate of SBI in healthy young adults has been previously studied, control subjects are not necessary in the present study and their inclusion would introduce added cost and ethical complications if MRI revealed other clinically meaningful incidental findings that required medical follow-up or intervention in these asymptomatic individuals.

2. Study Design and Statistical Procedures.

This will be a single-group observational study of the radiological entity SBI in very young adults (ages 25 to 40 years) who have had type I diabetes for at least 10 years and have never had a clinical stroke or TIA. Patients will be recruited from endocrinology clinics at Columbia University Medical Center (CUMC) using flyers. The primary outcome will be SBI. From the discussion above, the expected percentage of patients with SBI is 38 percent.

The study will enroll 26 young adults (ages 25 to 40 years) who have had type I diabetes for at least 10 years and have never had a clinical stroke or TIA. The number of subjects was determined using a one-sample chi-square test with an expected group proportion of

SBI of 0.38 compared to the published mean proportion of SBI of 0.125 in healthy young adults, with alpha set to 0.05 and power set to 0.8. The primary outcome is a proportion and does not require any further statistical analyses.

3. Study Procedures.
MRI without contrast will be performed as subjects are enrolled. The MRI procedures to evaluate for the presence of SBI will be the same as those described in a previous study by Dr. Joshua Willey and colleagues at CUMC (Willey et al., 2011). Briefly, MRI imaging will be performed on one 1.5 Tesla MRI machine. The presence or absence of brain infarction will be established from the size, location, and imaging characteristics of the lesion. As in Willey et al. (2011) and most recent papers on the topic, SBI will be defined as a cavitation on the fluid-attenuated inversion recovery sequence of at least 3 mm in size, and distinct from a vessel due to the lack of signal void on T2 sequence, and of equal intensity to CSF. This is consistent with the recommendations of a recent review on the MRI definition of SBI (Zhu et al., 2011).

4. Study Drugs or Devices.
There are no drugs or devices to be tested in this study.

5. Study Questionnaires.
No questionnaires will be included in this study.

6. Study Subjects.
Inclusion criteria:
--Age 25 to 40 years old.
--Type I diabetes diagnosis made at least 10 years earlier.

Exclusion criteria:
--History of stroke or TIA.
--History of other major neurological disorder that would impact MRI findings (multiple sclerosis, frontotemporal dementia, early onset Alzheimer's disease, traumatic brain injury).
--Device or other implanted metal item that would interfere with MRI.
--Moderate or severe claustrophobia that would prevent comfortable MRI experience.
--Unwillingness to have primary care physician contacted if MRI reveals an incidental finding that necessitates clinical follow-up (such as brain masses concerning for malignancy).

7. Recruitment.
Subjects will be recruited from the endocrinology clinic with flyers. After the patient contacts the investigators, the investigators will confirm with each patient's primary physician that the patient is suitable for the study.

8. Confidentiality of Study Data.
Individual patient information will have be coded and unique code numbers will be generated for each subject. The management and security of data will be addressed in

accordance with institutional standards of patient confidentiality. Data will be stored in a secure location and will only be accessible to the investigators.

9. Potential Risks.
MRI has no known risks or side effects. It has not been proven to be safe in pregnancy, though MRIs are typically not avoided during pregnancy when clinically indicated. Since participation in this study is not clinically necessary, women will not undergo MRI while pregnant. Thorough pre-MRI screening for devices that may be affected by the magnetic field, such as hearing aids and pacemakers, will be completed for all patients in accordance with standard practices. There is a remote chance that MRI will reveal an incidental finding that necessitates further clinical assessment or intervention. This risk will be explained to all participants and their consent will be obtained to contact their primary care physician in the event that this occurs.

10. Potential Benefits.
Individual patients will not benefit from participation in this study. This will be explained to patients when they consent to participate in the research.

11. Alternative therapies.
Not applicable.

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