

Evaluation of Neuropsychometric Outcome in Patients Undergoing Excision versus Stereotactic Radiosurgery for Cerebral Arteriovenous Malformations

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A. Study Purpose and Rationale

Cerebral arteriovenous malformations (AVMs) are estimated to be present in 40 million people worldwide. They are characterized by direct shunts between the arterial and venous system without an intervening capillary bed (1). Currently, many questions still remain concerning the development and natural history of cerebral AVMs, although it is believed that they represent a vascular dysmorphogenesis in the cerebral circulation that occurs during the embryonic period. In about 12% of patients, AVMs present with symptoms such as intracranial hemorrhage, seizures, focal neurological deficits, bruits, headaches, and mental changes. Current therapeutic options typically involve operative excision (with or without adjunctive endovascular embolization), stereotactic radiosurgery, or endovascular embolization alone. There is no consensus on an algorithm by which to determine optimal treatment and treatment of choice generally depends on several factors, including size, location, symptomatology, and the experience of the surgeon. While excision results in removal of the AVM and immediate cessation of the risk of hemorrhage, obliteration of an AVM may take up to 3 years following treatment by radiosurgery, during which time the risk for hemorrhage persists (2).

In general, the mental changes associated with cerebral AVMs are poorly understood. One theory is that the phenomenon of cerebrovascular steal may result in diversion of normal blood flow from regions of the brain surrounding the AVM, leading to "progressive regional ischemia" (3). Previous studies have demonstrated that cerebral AVM patients demonstrate a predictable pattern of neurobehavioral change, presumably arising from cerebrovascular steal (4). Metabolic studies have indicated that cerebral metabolic rates are significantly reduced in patients with AVMs, and that the overall metabolic rate is greatly enhanced following excision of the lesion (5). While the deleterious impact of an AVM on metabolic rate was most pronounced in the hemisphere ipsilateral to the lesion in these studies, the contralateral hemisphere was also shown to be affected. Mahalick et al. (3) conducted a study of 14 right-handed patients with cerebral AVMs in which they examined neuropsychological function at 2 days preoperatively and 7 months post-operatively. Using the San Diego Neuropsychological Test Battery they found that overall pre- and postsurgical performances were significantly worse in AVM patients when compared to normal controls. Grouping the results of the individual neuropsychological tests into 17 related groups and comparing the mean results for each group pre- and postsurgically, the authors found that 15 of these 17 groups showed improvement following resection of the AVM, with 45% of the comparisons reaching statistical significance ($p < 0.05$). The authors' concluded that "beneficial neuropsychological effects secondary to resection of the arteriovenous shunt provides good reason for re-evaluating the indications for therapeutic intervention". In a more recent study, 95 patients with cerebral AVMs treated by radiosurgery were assessed prospectively up to 3 years following treatment to evaluate their long-term cognitive function (6). No cognitive declines were found during follow-up, but significant improvement in neuropsychological test scores of IQ, attention, and memory were evident, with test scores approaching normal average test values.

To further explore the relationship between AVMs and neuropsychological impairment, we intend to prospectively follow patients receiving treatment via either excision (with or without adjunctive endovascular embolization) or stereotactic radiosurgery at CUMC and assess neuropsychometric outcome at various time points to 3 years post-treatment. To our knowledge, no previous study has examined neuropsychometric outcome in these two populations of AVM patients in parallel. Our hypotheses are that we will: (a) observe significantly worse pre-surgical neuropsychometric test (NPMT) performance in

AVM patients compared to control subjects; (b) that we will observe a significant improvement in overall neuropsychometric test performance in both populations following treatment; (c) that the time course for this improvement will vary between the two treatment groups, with the excision group exhibiting a relatively rapid improvement in neuropsychometric outcome that then levels off, while the group treated with stereotactic radiosurgery will have a slow steady improvement, reaching maximal improvement between 2-3 years; and (d) that the two treatment groups will exhibit similar overall mean changes in neuropsychometric outcome at 3 years following treatment.

B. Study Design and Statistical Procedures

I. This study will be a prospective observational longitudinal study of neuropsychometric outcome in patients undergoing primary treatment for a cerebral AVM. Study subjects will fall into two groups: (a) those treated via excision (with or without adjunctive endovascular embolization) and (b) those treated via stereotactic radiosurgery. The decision of which treatment each subject will receive will be made by the treating physician based on clinical factors. Currently there is no standard formula by which one can easily conclude an ideal mode of therapy for any given AVM. However, in general, the most effective method of treatment for small (<6cm), superficial AVMs in non-eloquent regions of the brain is operative excision. Currently, surgery is often preceded by adjunctive endovascular embolization to make the excision safer. Stereotactic radiosurgery is generally reserved for patients with small (<2.5cm) lesions located in areas of the brain that are not easily accessible by conventional means. Due to the differing clinical indications for these AVM treatments, it will not be possible to randomize subjects to one treatment or the other. The treating physicians will decide which modality of treatment the subject will receive. As a result, in our study the two treatment groups may have significant differences with respect to certain aspects of their disease, particularly, but not limited to, size and location of the AVM. These may have effects on baseline and follow-up NPMT scores for each treatment group, both overall and when examining subsets of NPMT, since lesions in certain locations may affect certain cognitive functions more than others (i.e. lesions in the dominant parietal lobe would be expected to have more pronounced effects on verbal tasks). This must be kept in mind when making conclusions based on the analyses of our study data.

II. Statistical analysis will be as follows. Demographic data including age, race, sex and description of surgery will be summarized. Surgical data will be recorded. In this study, our primary outcome will be the mean change in overall NPMT scores from baseline for the two AVM treatment groups at 3 years following their procedure. From previously published studies examining neuropsychometric outcome in both operative and stereotactic radiosurgery we expect both groups to show significant improvement from baseline NPMT scores. No prior study has examined this subtle change in cognition for these two treatment groups in parallel using the same battery of neuropsychometric tests that we will be using in our study. As such, the degree of improvement in overall NPMT score from baseline that will be exhibited by each group is unknown. For this study, we will use a battery of 6 validated neuropsychometric tests. A composite overall NPMT score will be developed that will generate a score from 0 to 80 (a higher score being better; see study procedures, below). We will define a clinically significant difference in the mean change of overall NPMT score from baseline between the two treatment groups to be an absolute difference of 1.0 on this scale. For instance, this would correspond to a difference of 6 more items identified correctly on the Boston Naming Test, 6 more words given in the Controlled Oral Word Association Test, or a difference of 30 seconds in either portion of the Reitan Trails Making Test or Grooved Pegboard Test. In performing our sample size calculations, we assumed equal variances in our study groups equal to 3.0 on our overall NPMT scoring scale. Our sample size calculations were based on this level of variance, the above effect size, a significance level of 0.05, and a desired power of 0.8. These calculations indicated that we will need to enroll 48 patients in each AVM treatment arm. Correcting for approximately 20% losses to follow-up (loss of contact with subjects, refusal to continue participation, neurologic morbidity resulting in inability to complete testing on follow-up, development of severe pain, depression, or anxiety that confounds neuropsychometric testing, and

death) we will be attempting to enroll 60 subjects into each of the treatment arms. At CUMC, approximately 6-10 patients are treated for cerebral AVMs each month. Based on this rate, we expect that it will be feasible to enroll the required number of subjects into our study within a period of 2 years. Each subject will then be followed for a total period of 3 years, with QOL questionnaires, depression/anxiety screening, neurological, and neuropsychometric examinations conducted at baseline (prior to treatment), 6 months, 1 year, 2 years, and 3 years following treatment.

III. Building on our primary analyses we will conduct secondary analyses to examine the mean change in overall NPMT scores from baseline for each of the two AVM treatment groups at follow-up time points of 6 months, 1 year, and 2 years. These analyses will be conducted using a repeated-measures analysis of variance (ANOVA) for unpaired data at a significance level of 0.05.

III. In order to assess the impact of cerebral AVMs on baseline cognitive function prior to treatment, mean overall NPMT scores for each of the treatment groups will be compared to a cohort of control subjects. Control subjects will be enrolled from the population of patients scheduled to undergo laminectomy surgery at CUMC that are age 18 or older and are able to provide informed consent. The same set of exclusion criteria applied to our study subjects will be applied to these controls. This group was chosen for controls since they do not have cerebral AVMs and are not expected to have cognitive impairment from their disease. Compared to normal controls, however, they are expected to have some neuropsychometric changes as a result of apprehension about their procedure. Also, it will be easier to retain these patients, compared to normal controls, for the study period needed. This makes laminectomy patients better candidates for comparison to our AVM treatment groups. Control subjects will undergo the same screening, neurological and neuropsychometric examinations as study subjects and will be followed for a period of 3 years with testing occurring at the same time points as study subjects. We will attempt to enroll controls to obtain a ratio of 1:1:1 control:excision: radiosurgery subjects in our study. We will perform secondary analyses examining the differences in mean overall NPMT scores between the AVM subjects in each treatment arm to controls at baseline and at each follow-up time point. These analyses will be conducted using repeated-measures analysis of variance (ANOVA) for unpaired data at a significance level of 0.05. The results of these analyses will allow us to determine if subtle cognitive deficits are present at baseline in AVM patients compared to controls, and will help to elucidate the time-course and degree of change in these deficits following treatment by either excision or radiosurgery.

IV. Lastly, we will examine the impact of several categorical variables on baseline neuropsychometric function and improvement in neuropsychometric function from baseline at the study end-point (3 years) in each of our study groups. The variables of interest will be age (categorized as less than 65 or greater than 65), size (categorized as <3cm, 3-6cm, and >6cm), and location (categorized based on lobe of the brain and dominant versus non-dominant hemisphere). This analysis will be conducted using a Chi-Square or Fisher's Exact Test as appropriate at an $\alpha=0.05$ level of significance to determine if significant associations exist. As part of this protocol, we would also like to more closely examine the relationship of AVM location to categorized subgroups of neuropsychometric tests (such as tests associated with aspects of language function, verbal memory, spatial memory, and fine motor manipulation, etc.) at baseline and at 3 years following treatment. Detailed information regarding the location of AVMs in study subjects will be available from clinically indicated CT, MRI (conventional and occasionally functional MRI) and angiography. This will enable us to closely correlate location and function as determined by performance on NPMT in our study subjects. Analyses will be performed via Chi-Squared, Fisher's Exact Test, or other *post-hoc* analytical methods as appropriate to the data available.

C. Study Procedures

In this study no experimental drugs or procedures will be utilized. The decision of when and which method of treatment (excision or radiosurgery) each study subject will have will be determined in the usual method by the treating physician based on clinical indications. Likewise, treatment of control subjects will be based on the clinical judgment of the treating physician. The study protocol will not affect

these decisions in any fashion. All subjects enrolled in this study will have clinical procedures conducted per standard of care and routine perioperative and follow-up care. The risks and benefits of any clinically indicated procedures will be explained to study participants by the treating physician(s) and/or staff. If specific concerns of subjects are voiced to study personnel, they will be brought to the attention of the treating staff. All patients will have routine perioperative and follow-up care.

Study procedures will include depression and anxiety screening and neuropsychometric testing at various time points (baseline and 6 months, 1 year, 2 years, and 3 years following treatment). Neuropsychometric tests are not intended to be diagnostic of specific neuropsychiatric disorders, but rather are designed to demonstrate general neuropsychological pathology. In previous studies we have developed a set battery of tests to assess this pathology (7,8). These tests can be divided into four types: (a) an evaluation of language, (b) an evaluation of speed of mental processing, (c) an evaluation of ability to learn using a list of words, and (d) an evaluation of visual perception requiring a patient to copy a complex figure.

Prior to beginning our neuropsychometric test battery, we will administer the Nelson Adult Reading Test (9). This is a premorbid IQ test which asks the patient to pronounce 45 printed words. It will be performed only at baseline and any subject at least 2 standard deviations below the national mean will be excluded from the study, as it has been shown that low premorbid IQ can affect neuropsychometric test results. Subjects will also be excluded from the study on the basis of concomitant Axis I psychiatric disorder, however we will additionally screen subjects for current depression or anxiety that may confound the NPMT results prior to administering the test battery. Screening for depression will be through completion of the Center for Epidemiologic Studies Depression Scale (CES-D) (10), which has been validated in previous studies (11). This scale consists of having the subject complete a form with 20 simple questions relating to depressive symptoms with a possible range of scores from 0-60. Patients with scores of 16 or more are considered depressed. Since depression can affect performance on neuropsychometric tests, patients that will be excluded from the study if they score 16 or more at any of the study time points. Screening for excessive anxiety will be via completion of the Hamilton Anxiety Scale (HAM-A) (12). This consists of having the examiner score 14 separate questions, 13 of which are based on responses from the subject, and 1 based on the subject's behavior during the interview. Possible scores range from 0-30, with scores <17 indicating mild anxiety, 18-24 mild to moderate anxiety, and 25-30 moderate to severe anxiety. Subjects scoring 18 or more on the HAM-A at any of the study time points will be excluded. In both cases, subjects will be made aware of the results of the screening tests, and if desired, contact information of physicians that can help in obtaining treatment for depression or anxiety will be made readily available. Finally, since it has been shown that pain can confound neuropsychometric testing we will assess the subject's level of pain while sitting and standing using a 10 point Visual Analog Scale before beginning the test battery (13).

The specific neuropsychometric tests that will be used in this study are as follows:

- a) Boston Naming Test: This test evaluates an important component of language and involves naming of 60 standardized pictures of items and animals. A maximum of 20 seconds is allowed for naming of each picture. A score is obtained from 0-60 (higher score is better).
- b) Controlled Oral Word Association (COWA) Test: This test evaluates the ability of a patient to say a list of words beginning with a specific letter in one minute, as another component of language. The different letters will be used in a row, for 3 letters in 3 minutes. The subject's score is the total number of correct and unique words to a maximum of 60 (higher score is better).
- c) Reitan Trail Making Test (Parts A and B): This test measures the time a subject takes to connect circles numbered from "1" to "25" with a straight line by pen or pencil in sequential order (Part A). Part B involves an added level of complexity in that it requires the subject to connect circles labeled with numbers or letters in an alternation fashion (i.e. "1" connects to "A" connects to "2" connects to "B", etc.). Performance on these tests is dependent on attention. A maximum time limit of 5 minutes is allowed per part. Scoring is the number of seconds it takes to complete the test (lower score is better).

- d) Rey Complex Figure Test: We will conduct both the Copy and Immediate Recall portions of this test, which measure the ability of a patient to copy a complex figure with pencil on paper and then immediately recall that figure from memory, as a non-dominant parietal lobe function. For each portion of the test, scoring will be from 0 to 36 (18 scoring units ranging from 0 to 2), where a higher score is better.
- e) Hopkins Verbal Learning Test (HVLT): This is a verbal memory test in which the subject is asked to immediately recall a standardized list of 12 items. The number of words remembered is recorded, and the test is then repeated twice more (HVLT Recall). Scoring for this portion is the number of items remembered correctly, to a maximum of 36 (higher score is better). At the end of the neuropsychometric battery, the subject will be asked to recall all 12 items again, this time without repeating of the list (HVLT Delayed Recall). The score for this portion is the number remembered correctly, to a maximum of 12. Lastly, a list of 24 words will be read to the patient, 12 of which are from the original list and 12 of which are distractors (6 being semantically related to the original 12). This portion is known as HVLT Recognition and results in a score from -12 to 12. A composite score from 0-60 will be determined by summation of these individual scores (scores less than 0 will be counted as 0).
- f) Grooved Pegboard Test: This test measures the time it takes for a subject to place twenty-five notched pegs into mirror-image holes arranged in various orientations, as a component of finger/hand manipulation. Each hand is scored separately. Scoring is the number of seconds it takes to complete the test, with a maximum limit of 5 minutes (lower score is better).

These scores will be adjusted obtain a composite overall NPMT score. First, we will convert the scores for each part of the Reitan Trails Making Test and Grooved Pegboard Tests to positive values. This will result in a score of 0-300 for each part of the Reitan Trails Making Test. Second, individual scores for tests 1, 2, 4 and 5 will be standardized to a score out of 10. Scores for each portion of the Reitan Trails Making Test and each portion of the Grooved Pegboard Test will also be standardized to a score from 0-10. Each of these scores will then be summed to yield an overall NPMT score from 0-80.

Study subjects and controls will be given the option to be admitted to the Irving Clinical Research Center (CRC) the day prior to their surgery when contacted by phone by study personnel. For those choosing to be admitted to this facility, written consent will be obtained and baseline depression/anxiety screening and neuropsychometric testing will be performed the day prior to surgery. For subjects choosing not to be admitted to the CRC, written consent will be obtained and baseline depression/anxiety screening and neuropsychometric testing will be performed the morning of surgery. Follow-up screening and NPMT will be conducted at 6 month, 1 year, 2 year, and 3 year time points. Whenever possible, testing will be scheduled to coincide with clinical follow-up appointments. In the event that it cannot, specific appointments will be set up for subject to have follow-up testing at CUMC, or in exceptional circumstances, at their place of residence with their permission.

D. Study Drugs

No study drugs will be administered during the course of this study.

E. Medical Device

No medical devices will be investigated during the course of this study.

F. Study Subjects

Based on our sample size calculations and an annual rate of approximately 6-10 AVMs treated by CUMC neurosurgeons each month (3-5 by excision and 3-5 by radiosurgery) we expect to actively enroll patients for approximately 2 years. Each patient will be enrolled for a total of 3 years, resulting in a total study duration of 5 years. We anticipate that the demographic of our study subjects will mirror that for

AVM patients being treated at CUMC and enrollment will be conducted independent of gender or ethnicity. This will result in approximately equal enrollment of males and females, 95% of subjects being between 18-65 years of age with 5% >65. Ethnic distribution will be approximately 25% African-American, 5% Asian, 38% Caucasian, 28% Hispanic, 2% Native American, and 2% Pacific Islander. Control subjects will be enrolled from a similar demographic population of patients at CUMC that are scheduled for laminectomy surgery. Control subjects will also be followed for a total of 3 years, however, approximately 20-30 laminectomy surgeries are performed each month. Based on our study design of 1:1:1 ratio of control:excision:radiosurgery subjects, we anticipate active enrollment of control subjects will be completed well within the 2 year active recruitment period for AVM subjects.

Inclusion Criteria: For control subjects inclusion criteria will include all patients undergoing elective laminectomy at CUMC that are able to provide informed consent. For AVM subjects, inclusion criteria will include all patients with a confirmed diagnosis of cerebral AVM undergoing primary elective treatment via either operative excision (with or without adjunctive endovascular embolization) or stereotactic radiosurgery that are able to provide informed consent.

Exclusion Criteria: For both controls and AVM patients, exclusion criteria will include: (1) Belonging to a vulnerable population (minors, pregnant women, cognitively-impaired, or institutionalized individuals); (2) History or development of permanent neurological impairment; (3) History of Axis I psychiatric diagnosis; (4) Positive screen for depression or anxiety using the CES-D rating scale for depression or the HAM-A rating scale for anxiety, respectively, at baseline or at follow-up testing; (5) Non-fluency in the language in which testing is administered; (6) Previous treatment for the same or different AVM (i.e. previous excision or radiosurgery attempt, or embolization treatment of the current AVM prior to enrolling the patient and obtaining baseline study examinations); (7) Participation in a concurrent clinical trial.

G. Recruitment of Subjects

Prospective enrollees will be initially approached by the treating CUMC neurosurgeon or affiliated staff during a consult visit prior to their surgery. They will be informed about the study at this time and if interested, will be asked permission for a member of the study team to contact them by phone prior to their surgery. At that time, verbal consent will be obtained. The study personnel will then meet the patient the day prior to their procedure to review their history and conduct the baseline testing (for those choosing to be admitted to the Irving CRC). For patients electing to undergo same-day procedure, the study personnel will meet the patient in the morning before the procedure to review their history and perform baseline testing.

H. Confidentiality of Study Data

A completely de-identified database will be constructed. De-identification will involve the replacement of direct patient identifiers from data sets with a linking code by which the data remain identifiable. For linking purposes, we use study-specific codes, rather than medical record numbers, Social Security numbers, or other easily decoded combinations of initials and birth dates. More specifically, all clinical data and follow-up information will be locked in a secure metal file cabinet with only the principal investigator (PI) and co-investigators having keys. Digital files will be maintained on the PI's computer with password protection. Access to the linking files will be restricted to the PI, co-investigators, and members of the research team at Columbia University, and only given on an as-needed basis.

I. Potential Conflict of Interest

None of the investigators or the University has any conflicts of interest associated with this study.

J. Location of Study

The recruitment of patients, administering of tests, and recording and storage of data associated with this study will take place within the departments at CUMC involved in the clinical care of the enrollees, namely, the Departments of Neuroanesthesiology (Dr. E. Heyer), Neurosurgery (Dr. R. Solomon), and Interventional Neuroradiology (Dr. J. Pile-Spellman). In exceptional instances, study personnel may travel to the subject's home with their permission to conduct study examinations.

K. Potential Risks

There are no potential risks associated with participation in this study.

L. Potential Benefits

The only direct benefit associated with participation in the study is information obtained during screening for depression and anxiety at baseline and study follow-up time points that might not otherwise be performed. Participation in this study has an indirect benefit of helping healthcare practitioners better understand the implications of AVM treatment on cognitive outcome and may be useful in guiding treatment for cerebral AVMs in the future.

M. Alternative Therapies

The alternative to participating in this study is to have treatment without additional QOL assessments, depression/anxiety screening, neurologic, and neuropsychometric examinations. The decision whether to participate in this investigation is voluntary and will not affect their medical treatment.

N. Compensation to Subjects

Subjects will be compensated travel costs to each follow-up visit at CUMC for study purposes following their treatment (up to a maximum of \$5 per follow-up). Payment will be made in the form of a check following the visit.

O. Costs to Subjects:

Costs to subjects will include the cost of traveling to CUMC (which will be offset by the above compensation), and loss of pay for any work that they miss due to follow-up visits to CUMC. When possible, examinations conducted for this study will coincide with scheduled clinical follow-ups. In exceptional instances, study personnel may travel to the subject's home with their permission to conduct study examinations in order to minimize this cost.

P. Minors as Research Subjects:

No minors will be enrolled in this study.

Q. Radiation or Radioactive Substances:

No radiation or radioactive substances will be used for the purposes of this study. Stereotactic radiosurgery will be conducted as standard of care for the treatment of cerebral AVM in a subset of study subjects. The determination of which subjects will receive radiosurgery will be based solely on clinical grounds and will be determined by the treating physician. As such, risks and benefits of the radiation

exposure associated with radiosurgery will be discussed during the consent process for the clinical procedure prior to enrollment in this study.

R. References

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