Summary Protocol

Untreated Clinical Course of Cerebral Cavernous Malformations: an individual patient data meta-analysis

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Institutions
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Research problem
Publications from the Scottish Intracranial Vascular Malformation Study (SIVMS, www.saivms.scot.nhs.uk)\textsuperscript{1}, the Mayo Clinic (www.mayoclinic.org/central-nervous-system-vascular-malformations)\textsuperscript{2}, the Toronto Brain Vascular Malformations Study Group (http://brainavm.oci.utoronto.ca)\textsuperscript{3} and others (Figure) constitute the best knowledge available about the prospective risks of intracranial haemorrhage and non-haemorrhagic focal neurological deficits in patients with cerebral cavernous malformations (CCM). These papers also identify risk factors for symptomatic events. However, as pointed out in accompanying editorials\textsuperscript{4, 5}, there remain important uncertainties regarding the natural history of people with untreated CCM. All published studies to date have been based on relatively small sample sizes, so that even when risk factors are identified consistently (e.g. the importance of a prior haemorrhage in determining the risk of a future haemorrhage), the magnitude of the effect has not been estimated with precision. For other putative risk factors (e.g. patient sex or the location of the CCM), the literature is inconsistent.

We propose an individual patient data meta-analysis of the prognosis of untreated CCM to address these outstanding uncertainties. By pooling data from several large studies, we shall be able to quantify known risks with much greater precision and develop a consensus over putative risk factors. Ultimately we shall develop and evaluate/validate a prognostic model based on several covariates. Although not a specific aim of the first phase of this collaboration, the exercise of assembling the data from several cohorts will also allow us to assess whether it would be feasible to address some even more challenging questions, including the impact of pregnancy and antithrombotic drugs on the risk of clinical events, and to identify risk factors derived from imaging.

Challenges
The precise research questions which can be addressed will depend on many factors, including the variation in the design of the different constituent studies (for example, at what point in their clinical course patients were recruited into the study; whether follow-up time can be split as pre-treatment and post-treatment, where applicable; and what systems are in place for follow-up), and the types of events (whether any symptomatic neurological events were recorded or only haemorrhagic events, and whether these events are confirmed by brain imaging). Equally, the statistical power of our analyses will be limited by the number of outcome events that can be included; this will also shape the research questions that can be addressed.
Approach

We plan, therefore, to adopt a two-step approach to the project. In a first exploratory phase, we shall identify collaborators, gather background information on the relevant study designs and databases, and accumulate the data centrally. In the second phase, we shall refine the scientific protocol, based around the practical constraints of what research questions can be addressed, given the strengths and limitations of the assembled data, with the input of our collaborators. To avoid the perception that the analysis is ‘data driven’ we set out the primary and secondary objectives below, although we recognise that the detailed scientific protocol can only be finalised in the light of the results of the first phase of the work.

The intention is to complete as much as is possible of the first phase in time to inform discussions at the first investigator meeting to be held in Edinburgh in September 2012, around the time of the AVM Conference (18-19 September) or ESNR Annual Meeting (20-23 September).

Objectives

Primary Objectives

- **Descriptive analysis of time-to-event outcomes.** Outcomes during untreated follow-up will include intracranial haemorrhage (ICH), but also focal neurological deficit (FND) or a composite endpoint of ICH or FND, if the data have been recorded in such a way as to permit this. In addition, we will examine event rates over long periods of follow-up to ascertain whether the estimated risk remains constant, or whether it diminishes over several years.
- **Identification of risk factors.** In most studies a prior ICH has been identified as a risk factor for a future ICH, but the magnitude of this effect is uncertain; sex, CCM location, and possibly age are the other putative risk factors, which we will examine if there is sufficient power (i.e. enough outcome events).
- **Building and evaluating a multivariate prognostic model.** The model will be used to predict the probability of a future ICH (± FND, if the data are available) for an adult with CCM(s) during untreated follow-up. Pre-specified covariates in the model will be chosen for clinical significance and will include prior ICH/FND, sex, CCM location and possibly age.

Secondary Objective

- **Exploring potential for future work.** For example, what is the effect of pregnancy on the untreated course of the disease; what is the effect of antithrombotic therapy on adults with untreated CCM; does CCM size influence disease outcome; how does treatment (with neurosurgical excision or stereotactic radiosurgery) affect outcome?

Methods

**Eligibility criteria for study cohorts**

- Each study should have a minimum sample size of 60 adults.
- Period at risk should begin at either (i) first CCM diagnosis (‘date of diagnosis’), or (ii) symptoms leading to it (‘date of clinical presentation’), thereby enabling calculation of event risk (not retrospective ‘lifetime risk’) at standardised time-points in the disease course.
- ICH should be included as an objective pre-defined clinical outcome.
- Outcome events should be able to be quantified per patient during the follow-up period.

**Eligibility criteria for patients within study cohorts**

- Adults who have received a first-ever CCM diagnosis.
- Diagnosis validated either by brain MRI or pathological examination.
- Patients to have some untreated follow-up time to contribute to the study.
Types of outcome measures

Although ICH is the primary outcome measure in this study, it is important to include in our analysis, wherever possible, adults who suffer non-haemorrhagic FNDs – either as a separate outcome measure, or as a secondary composite endpoint. Both ICH and FND have a similar level of severity for the patient, and in certain circumstances an outcome labelled FND may, in reality, be an ICH, but not categorised as such, either because the appropriate neuro-imaging was not performed or because the imaging failed to detect any blood.6

Analysis

In this study, our sole interest is the untreated course of the disease: thus adults who have received some form of interventional treatment will contribute data to the survival analyses only until the date of first treatment, at which point their data will be censored. Data will be censored at the earliest occurrence of any of the following: death unrelated to CCM; treatment (whether surgery or stereotactic radiotherapy); last available follow-up.

Fundamentally, we will perform analyses within studies and pool the results (e.g. an estimated hazard ratio or an estimated adjusted hazard ratio) using forest plots and random effects meta-analysis.

References

Figure 1 Risk of symptomatic intracranial haemorrhage during follow-up in studies of the untreated clinical course of > 20 participants with cerebral cavernous malformations

Areas of point estimates are proportional to the sample size of each study. Error bars represent 95% confidence intervals (if available or calculable). Listed studies are included in the References (1-3, 7-19).

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<th>Study</th>
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