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The nature, frequency and natural history of intracranial cavernous malformations in adults

Julie Maria Hall
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<tbody>
<tr>
<td>AVM</td>
<td>arteriovenous malformation</td>
</tr>
<tr>
<td>BBB</td>
<td>blood brain barrier</td>
</tr>
<tr>
<td>CCM</td>
<td>cerebral cavernous malformation</td>
</tr>
<tr>
<td>CM</td>
<td>cavernous malformation/cavernoma</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebro-spinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
</tr>
<tr>
<td>FND</td>
<td>focal neurological deficit</td>
</tr>
<tr>
<td>GRE</td>
<td>gradient echo</td>
</tr>
<tr>
<td>GRO</td>
<td>General Register Office</td>
</tr>
<tr>
<td>IADSA</td>
<td>Intra-arterial digital subtraction angiography</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases - 10</td>
</tr>
<tr>
<td>ICH</td>
<td>intracranial haemorrhage</td>
</tr>
<tr>
<td>ICM</td>
<td>intracranial cavernous malformation</td>
</tr>
<tr>
<td>ISD</td>
<td>Information and Statistics Division</td>
</tr>
<tr>
<td>IVM</td>
<td>intracranial vascular malformation</td>
</tr>
<tr>
<td>LINAC</td>
<td>Linear Accelerator</td>
</tr>
<tr>
<td>LREC</td>
<td>Local Research Ethics Committee</td>
</tr>
<tr>
<td>MREC</td>
<td>Multi Centre Research Ethics Committee</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>SAIIVMS</td>
<td>The Scottish Audit of Intracranial Vascular Malformations</td>
</tr>
</tbody>
</table>
SIVMS.....................The Scottish Intracranial Vascular Malformation Study
SMR01.................................................Scottish Morbidity Records 01
SWI..................................................susceptibility weighted imaging
VM....................................................venous malformation
vEGF...............................................vascular endothelial growth factor
Preface

This thesis developed from my period as Research Fellow with the Scottish Intracranial Vascular Malformation Study (SIVMS), now known as the Scottish Audit of Intracranial Vascular Malformations (SAIVMS), a post held from April 2002 until August 2004. SIVMS was the first prospective, population-based study of the major types of intracranial vascular malformations; arteriovenous, cavernous and venous malformations including dural fistulae and carotid-cavernous fistulae. It was based in Scotland and designed in 1998 by my supervisor Professor Charles Warlow and the first Research Fellow Dr Rustam Al-Shahi supported by the SIVMS steering committee (www.saivms.scot.nhs.uk). Recruitment and follow-up began in January 1999. Recruitment and follow-up of all vascular malformation types was done by Dr Al-Shahi until March 2002 and this role then transferred to me in April 2002 until I left in August 2004. The main duties of the Research Fellow were to collect and review all the clinical material of cases notified to SIVMS and arbitrate with the relevant expertise where there was doubt whether the case met the criteria for inclusion in SIVMS. Apart from my clinical responsibilities in recruitment and follow-up, the post also involved supervision of the part-time study administrator and also weekly meetings with the study programmer. I was also responsible for convening and presenting updates of the study progress weekly to my supervisor Professor Charles Warlow, biannually to the Study steering committee meetings, and annually to my funding body, the Stroke Association. This Research Fellowship also allowed me to gain an appreciation of the efforts needed to sustain collaborators’
interest in a long running study and I made presentations to improve the profile of the study on the national and international stage.

For my duration as the SIVMS Research Fellow, I recruited and followed-up all types of newly diagnosed intracranial vascular malformations (IVMs). This thesis, however, is based solely on the incident intracranial cavernous malformations (ICMs) recruited to the study by both Dr Al-Shahi and myself between January 1999 and December 2003. The follow-up data in this thesis were that available to me on August 31st 2004. The data cleaning and the analysis for this thesis has been performed by me alone under the supervision of Professor Warlow.

Although the core study design was well-established and tested prior to my involvement with SIVMS, I did devise new studies such as the Sensitivity and Specificity of MRI in the diagnosis of intracranial CMs. This cavernoma imaging study was a separate study designed, executed and analysed by myself, a medical student Sue Liong, the Cavernoma Imaging Study Group [appendix 1] with guidance from Professor Warlow, Dr Al-Shahi, Dr Andrew Farrall (consultant neuroradiologist) and Dr Steff Lewis (Medical Statistician). Computing support was provided by Aidan Hutchison (SIVMS programmer).

The writing of this thesis has been done by me alone under the supervision of Professor Warlow. I therefore take ultimate responsibility for the contents of the
thesis. All graphs, tables and figures have been created by me unless a clear
acknowledgement lies underneath.

This thesis has also been the progenitor for a paper on the subject of the 5 year
untreated clinical course of cavernomas which has been published by Lancet
Neurology [Al-Shahi, 2012],[Appendix 14].
Acknowledgements

First and foremost I want to thank the patients in SIVMS without whom a study of this kind would not have been possible. During my time as SIVMS Research Fellow they showed enthusiasm, commitment and gratitude to the SIVMS team which was inspirational at times when faced with a mountain of casenotes to review! The Stroke Association funded my salary for the duration of the post and I will always be most grateful for the opportunity this provided. I also want to thank Rosemary Anderson, the study administrator with whom I shared an office for two and a half years, and Aidan Hutchison the study programmer, for their hard work, dedication to detail and friendship. I cannot stress how grateful I am to my supervisor, Professor Charles Warlow, who came out of retirement to continue to support me in the creation of this thesis. His suggestions on my drafts inspired by sailing around the Western Isles have been most helpful.

Last, but definitely not least, I want to thank my husband Roger, children; Fergus, Jennifer and Samuel, and my parents whose unflinching support, encouragement and love inspired me to complete this thesis.
Abstract

Background: Intracranial cavernous malformations (cavernomas) are an abnormal collection of dilated vascular channels in the brain. Their aetiology is complex and largely unknown but they can cause significant morbidity and mortality in terms of epilepsy, haemorrhage and focal neurological deficit (FND). The histopathology and also MR imaging characteristics are well described but the validity of MR as a diagnostic tool has never been evaluated.

Aims of this thesis: 1. To systematically review the literature on intracranial cavernous malformations in adults. 2. To establish the incidence, presentation and early untreated prognosis of intracranial cavernous malformations in a population-based study of adults in Scotland. 3. To evaluate the validity of MR imaging as a diagnostic tool for intracranial cavernomas.

Methods: A systematic, electronic search of the literature was carried out initially and all relevant articles were reviewed. The incidence, presentation and early prognosis of cavernomas were estimated in a cohort recruited to the Scottish Intracranial Vascular Malformation study (SIVMS) between January 1999 and December 2003. The sensitivity and specificity of MR imaging was estimated in an independent study of pathologically verified cavernomas and imaging mimics.

Results: Systematic review of the literature revealed a paucity of methodologically robust evidence on the natural history of intracranial cavernomas in adults. The incidence of intracranial cavernomas in adults in SIVMS was 0.67 (95% CIs, 0.56 to 0.79) per 100,000 adults per year. The presentations in SIVMS, in decreasing order
of frequency were; asymptomatic (47%), epilepsy (25%), focal neurological deficit (15%) and haemorrhage (13%). Being female or presenting with haemorrhage or FND appear to increase the risk of having a haemorrhage or FND during early follow-up. The all cause mortality in SIVMS was 13% at three years. The sensitivity and specificity of MR imaging varied between 58-83% and 67-100% respectively.

Conclusions: Intracranial cavernous malformations are rare lesions but have a significant morbidity and mortality associated with their diagnosis. MR is a valid diagnostic and screening tool for intracranial cavernomas.
Chapter 1:

Introduction
The nature, frequency and natural history of intracranial cavernous malformations in adults

1.1 Intracranial cavernous malformations (cavernomas)

Stroke is the third biggest cause of death in the UK and the largest single cause of severe disability [National Stroke Strategy, 2007]. Twenty-five percent of strokes are in people under the age of sixty-five. Strokes in young people are devastating not only for the victim but also their family. Intracranial cavernous malformations are one of the more rare causes of these debilitating events. They have also been responsible for the high profile death of an American track and field athlete Florence Griffith-Joyner in 1998 due to sudden unexpected death caused by epilepsy. To date the natural history of these lesions remains shrouded in mystery and their significance in terms of prevalence in a population is also unclear. This has been the inspiration for this thesis which focuses solely on intracranial cavernomas.

Histopathology has been, and remains, the gold standard in the diagnosis of intracranial cavernous malformations. There is consensus about many histological features of cavernomas but there is also a long running debate in the literature about one feature that, supposedly, distinguishes cavernomas from capillary telangiectases. In this chapter I will set the scene with an overview of the contribution histopathology makes to the diagnosis of cavernomas and, also, the literature on ultrastructure and immunohistochemistry. I will also review current views on the aetiology of intracranial cavernous malformations and the modern diagnostic techniques now available.
1.1.1 Histopathology

Intracranial vascular malformations are often macroscopically described as mulberry-like structures which microscopically are found to be composed of a collection of dilated vascular channels (figures 1 & 2).

Figure 1 Macroscopic appearance of an excised brain cavernoma
The nature, frequency and natural history of intracranial cavernous malformations in adults

Figure 2 Microscopic appearances of a brain cavernoma

These channels are described as thin walled structures lined by a single layer of endothelium but lacking a basement membrane, elastin and also smooth muscle. They are not encapsulated lesions but are well circumscribed closely knit structures that are surrounded by gliotic brain tissue and a variable amount of haemosiderin-laden macrophages [McCormick, 1966], [Simard, 1986], [Jellinger, 1986], [Zabramski, 1999] and [Raychaudhuri, 2005]. They also contain a variable amount of calcification and blood in various stages of thrombosis.

Discussion or disagreement in the literature arises over the necessity for the lack or presence of brain parenchyma interwoven with the vascular channels as a distinguishing feature between cavernomas and capillary telangiectases. The case for
The nature, frequency and natural history of intracranial cavernous malformations in adults

the absence of intervening brain parenchyma in cavernomas was first presented by Virchow in the mid 19th century [Virchow, 1851].

Support for it has been given throughout the years [Bergstrand, 1936], [Russell & Rubenstein, 1977], [McCormick, 1966], [Simard, 1986], [Jellinger, 1986], [Zabramski, 1999] and [Raychaudhuri, 2005]. These authors all subscribe to the present scheme of classifying vascular malformations which identifies cavernomas and capillary telangiectases as distinct entities. The only real reported histological difference between the two is the absence of intervening brain parenchyma in cavernomas and that is why this assumes such significance in classification systems. As a group, they acknowledge the existence of mixed vascular malformations but cannot decide whether they constitute a group of lesions that represent transitional forms between the different types of malformations with a common pathogenesis or, simply, that they signify the occasional coexistence of two different malformations in the same location. Some clinical differences between cavernomas and capillary telangiectases are also mooted which will be discussed later.

The main reasons cited for not placing both these lesions into one group are

1. The presence of larger, developmentally older lesions (i.e. cavernomas) in younger patients.

2. The presence of enlarged draining veins among most capillary telangiectases and an absence of similar veins among cavernous lesions.
The nature, frequency and natural history of intracranial cavernous malformations in adults

3. The tendency to haemorrhage which is restricted almost exclusively to cavernous malformations

4. The occasional presence of capillary telangiectases which are larger than cavernomas when they coexist.

The presence of intervening brain parenchyma in cavernomas was first published by Russell (1931) who suggested that capillary telangiectases could be precursors of cavernous malformations [Russell, 1931]. Her suggestion, that cavernomas were formed from the fusion of adjacent capillary loops, was a hypothesis also embraced by others who cited examples of a spectrum of transitional lesions between the two entities and also the frequent co-existence of the two lesions in a particular patient [Sjovall, 1938] & [Wyburn-Mason, 1944]. These authors believe that it is possible to have interwoven brain parenchyma within the core of cavernous malformations.

More recently, work published by Rigamonti and others stressed the common ground between the two groups [Rigamonti, 1987] & [Rigamonti, 1988]. Their specimens depicted the commonly reported mass of closely packed, sinusoidal-type vessels devoid of elastic and muscular fibres [Bogren, 1970], [McCormick, 1984], [Stehbens, 1972], [Zulch, 1965]. Iron deposition in macrophages and glial cells in and around the vascular lesion and evidence of thrombosis, calcification, haemorrhage, inflammatory changes and ossification were identified in decreasing frequency, consistent with published data [McCormick, 1984], [Russell Rubenstein, 1977] & [Stehbens, 1972].
What was more interesting was the frequency with which brain parenchyma was found between the abnormally dilated vascular channels in Rigamonti’s cohort - it was high at 35%. This allowed Rigamonti to suggest that the transitional forms between cavernomas (CMs) and capillary telangiectases are more frequent than previously thought and, therefore, that the division of CMs and capillary telangiectases into separate categories is arbitrary and inaccurate. He suggested that capillary telangiectases and cavernomas represent the ends of a spectrum of a single pathological entity and, therefore, proposed grouping them in a single category termed cerebral capillary malformations. Work by Tomlinson et al [Tomlinson, 1994] and also Frischer et al [Frischer, 2008] support Rigamonti’s finding of intervening brain parenchyma in lesions otherwise classified as cavernous malformations.

The arguments set out by the authors rallying against the need for the presence of intervening brain parenchyma are answered as follows:

1. Enlarged draining veins seen in association with capillary telangiectases but not with CMs [Blackwood, 1941] & [Russell Rubenstein, 1977]: This is now known to be false [Rigamonti, 1991], [Numaguchi, 1977].

2. The tendency of CMs only to bleed and cause important clinical symptoms [Russell Rubenstein, 1977]: This too is unsound as telangiectases can occasionally cause symptoms [McCormick, 1968] & [Teilmann, 1953].
3. Smaller lesions do not always have the telangiectatic pattern when multiple lesions are present. Rigamonti argues that this is because smaller vascular malformations most likely represent an early transitional form.

4. The presence of larger, developmentally older lesions (i.e. cavernomas) in younger patients: In the autopsy case from Rigamonti’s series, two CMs coexisted with 2 transitional capillary telangiectases, confirming the coexistence of these two lesion types [Roberson, 1974] & [Russell Rubenstein, 1977].

Although the case looks more and more convincing that from a pathological point of view perhaps these vascular lesions should be reclassified, Robert Solomon who comments on Rigamonti’s article made the valid point that reclassifying these lesions into the same group was not necessarily clinically helpful as currently telangiectases are not surgically removed but cavernomas in the correct clinical setting can be reasonably safely excised [Rigamonti, 1991]. Therefore reclassifying based on pathological definitions could serve the purpose of muddying the clinical waters in appropriately selecting cases suitable for surgery/treatment.

While there is consensus about most histopathological features of cavernomas there is still disagreement about the distinction between cavernomas and capillary telangiectases. This is mainly because the pathogenic mechanisms leading to
The nature, frequency and natural history of intracranial cavernous malformations in adults cavernomas are still shrouded in mystery. Much promise exists in this area, however, as a result of discoveries over the last 10 years, as discussed later.

1.1.2 Ultrastructural features of intracranial cavernous malformations

Merely three main studies have been published on the ultrastructural appearance of cavernous malformations [Wong, 2000], [Clatterbuck, 2001] and [Tu, 2005]. They include data from 3, 2 and 9 lesions respectively. Although the numbers are small they throw up potentially interesting features that may contribute to our understanding of the pathogenesis.

The cerebral microvasculature or blood-brain barrier (BBB) is a unique and essential structure that consists of the interplay of three major microvascular components. Tight junctions between endothelial cells constitute the major permeability barrier, and the overall biology of the barrier is shaped by the paracrine interactions of the endothelium with the pericytes/smooth muscle cells and the astrocyte foot processes that cover most of the abluminal surface of the microvasculature [Pardridge, 1999]. What all these studies suggest is that abnormalities of the blood brain barrier are important in the pathophysiology of cavernous malformations.

In blood-brain barrier (BBB) capillaries, endothelial cells are joined by continuous tight junctions produced in response to signals from astrocytes. In their small series Wong and others compared and contrasted cavernomas and arteriovenous malformations (AVMs) and demonstrated that, unlike AVMs, cavernomas have an
immature BBB with absent *tight junctions* between endothelial cells, no astrocytic foot processes and rare pericytes. This finding was reproduced by Clatterbuck et al and, interestingly, when Tu et al compared haemorrhagic cavernomas with non haemorrhagic cavernomas these deficient tight junctions were only present in haemorrhagic lesions. This raises the possible mechanism whereby low flow vascular lesions such as cavernomas bleed regularly and also provides a possible theory about how they grow by recurrent small bleeds.

These studies have also recorded haemosiderin staining in the tongue of normal brain tissue surrounding the lesion – presumably a blood breakdown product from frequent intermittent bleeds or leaks from the lesion. The absence of the basal lamina is also noted by Tu et al which is usually a feature of developing or immature capillaries. This was not a feature of Wong’s study but he did remark on the abnormality of the present basal lamina.

Early studies of cavernoma ultrastructure raise interesting theories about the potential pathogenesis of these lesions. Further similar work on larger case series should be helpful but electron microscopy is a costly and time consuming exercise and not strictly necessary for the management of patients in the short term. Therefore we may have to await this kind of study for some time.
1.1.3 Immunohistochemistry

There is an abundance of work on various proteins and growth factors in the literature on cavernomas, for example [Frim, 1996], [Robinson, 1995], [Rothbart, 1996] and [Notelet, 1997], but none have as yet provided a unifying theory for the pathogenesis of cavernomas. Therefore I think it is sufficient to acknowledge that this work is ongoing and someday may contribute to the bigger picture of cavernoma development/aetiology. One facet of this work that I do want to highlight is a study of the expression of oestrogen and progesterone receptors in cavernomas [Kaya, 2009]. There is a lot of literature constituting case reports and case series with small numbers, which suggest a relationship between pregnancy or hormonal therapy and the increased haemorrhage rate and seizure expression of cavernomas. In this context the study by Kaya et al [Kaya, 2009] was the first to look at the expression of the relevant hormonal receptors within cavernomas themselves as a way of explaining this phenomenon but they found no expression of oestrogen or progesterone receptors in any of the 12 cerebral cavernomas they examined.

1.1.4 Developmental venous anomalies or venous malformation (VM)

This is another form of intracranial vascular malformation. VMs are not abnormally formed venous channels but merely dilated vessels. In isolation they are of little consequence [Hon JM, 2009] but as will be apparent later in my thesis a proportion of cavernomas are associated with a venous malformation (figure 3). The main
The nature, frequency and natural history of intracranial cavernous malformations in adults

significance of this is that the presence of both a CM and VM can make surgical excision more difficult. It suffices at this point just to know of their coexistence.

Figure 3 A venous malformation (arrow heads) accompanying a cavernoma (arrow) on a contrast enhanced T1 weighted MR scan of the brain

1.2 Aetiology

1.2.1 Familial and sporadic cases

Previously it was thought that cavernomas were congenital lesions but this is now known not to be the case and this has significant implications for the estimation of lesion haemorrhage rates, as will be discussed later [Detwiler, 1997 & Zabramski, 1994]. In the last ten years there have been great strides in the mammoth task of
understanding the aetiology of cavernous malformations. It has seen the discovery of three genes involved in the familial form of the disease. Sporadic cases also occur, and cavernomas can develop de novo after treatment with radiotherapy anywhere from 2 to 20 years later. More often than not familial forms of the disease have multiple lesions of varying size and also varying symptomatology often within the same patient. There is well documented evidence of the dynamic nature of cavernomas in these patients. The size of documented lesions can increase over time with or without haemorrhage [Zabramski, 1994]. New lesions also appear over time [Zabramski, 1994]. It is now well established that familial cavernomas have an autosomal dominant pattern of inheritance with incomplete clinical and also neuroradiological penetrance. In the last 15 years three cerebral cavernous malformation (CCM) genes have been identified; CCM1/KRIT1 (chr 7q), CCM2 (chr 7p) and CCM3 (chr 3q) in decreasing order of frequency [Gunel, 1996], [Bergametti, 2005], [Laberge, 1999], [Sahoo, 1999], [Sahoo, 2001] and [Eerola, 2001]. A strong founder effect has been detected in Hispanic-American patients with cavernomas, with most families linked to the CCM1 locus [Gunel, 1996]. So far more than 150 distinct CCM1/2/3 germline mutations have been published [Riant, 2010]. More than 90 of those are mutations of the CCM1 gene and the remainder are divided between mutations of both the CCM2 and CCM3 genes. The proteins encoded by all three CCM1-3 genes, KRIT1, MGC4607 and PDCD10 have been identified but their detailed functioning is still not entirely clear. It appears however that ‘loss of function’ is the most likely pathophysiological mechanism resulting from these germline mutations.
Because cavernoma inheritance is autosomal dominant, the question arises what makes lesions occur focally and in multiple sites in the familial cases? Most groups subscribe to the theory of ‘Knudson’s two hit’ mechanism. A somatic mutation, possibly acquired in the embryonic or postnatal period, adds to the germline mutation resulting in the complete loss of the two alleles. Interestingly, somatic mutations occur only in endothelial cells and not in the intervening neural tissue. Also, not all endothelial cells of the lesion carry the somatic mutation. Therefore, it seems that lesions are comprised of a mosaic of wild-type and mutant endothelial cells.

Recent identification of proteins that interact with one or more of the CCM1, CCM2 and CCM3 proteins suggest that they influence angiogenesis in some way. Also CCM1 and CCM2 proteins have been shown to interact in vitro [Zawistowski, 2005] suggesting they form a molecular complex that probably involves MAPK and the p38 pathway. Whether CCM3 has a similar interaction remains to be seen. Recent in vivo studies on murine and zebrafish models when CCM1 and CCM2 were inactivated shed some light on their roles in cardiovascular development. Although both model embryos died at midgestation, before cerebral blood vessels had developed, it was clear that they are involved in arterial morphogenesis and differentiation during early embryonic life. If and when conditional mutants in which CCM genes specific to the central nervous system (CNS) are inactivated that can survive to full term are developed it will give exciting insight to the pathogenesis of cavernomas.
The identification of three CCM genes is an important step towards understanding the mechanisms of the disorder. These genes have helped clarify certain features of the disorder such as the incomplete clinical and neuroradiological penetrance of the familial form, as well as the molecular basis of ‘sporadic’ cases with multiple lesions. It will be down now to additional large series studies, like SIVMS, to further assess genotype-phenotype correlations, particularly prognosis in relation to the nature of the mutated gene. It is likely that there are, as yet, other unidentified genes in familial cases in whom no gene has been identified, or it is possible that sporadic single cases harbour a genetic defect as yet undeclared. Another possibility is that there may be a modifying gene explaining intrafamilial clinical variability.

Identification of CCM genes also means that molecular genetic screening is now possible. When screening all three genes in a CCM proband, sensitivity of genetic screening is 96% in patients with an affected relative, and 57% in sporadic cases with multiple lesions [Labauge, 2007]. However, once the mutation has been identified within a proband, sensitivity is 100% when screening relatives of the patient. This raises all sorts of questions about how molecular genetics screening affects clinical care of patients and their relatives. What are the indications for genetic and magnetic resonance imaging (MRI) screening in asymptomatic individuals? Is screening justified at all when there is no reliable evidence what the best management is for asymptomatic, or indeed symptomatic patients? Are patients better off not knowing? There are very real parallels between this situation and the hotly debated topic of screening relatives of patients with aneurysmal subarachnoid haemorrhage [Miller,
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2011]. Genetic screening should always be on a background of balanced risk-benefit ratio. This will not be an issue easily resolved and will lead to many earnestly argued debates in the future.

Truly sporadic cases of cavernomas are thought to harbour mostly single lesions, are not inherited and do not carry a CCM gene mutation. However, in all case series based on cases presenting clinically as sporadics, a significant proportion of the cohort have had multiple lesions when examined by gradient echo (GRE) MRI. It now appears that a sizeable proportion of this group is actually a result of genetic mutations whether undiscovered familial or new mutations. In a study done by Labauge et al [Labauge 1998] clinical and neuroradiological analyses done prior to the identification of CCM genes in a series of 22 consecutive sporadic cases with multiple lesions showed that 75% of them were affected with a hereditary form of the disease with incomplete penetrance because one of their two asymptomatic parents showed lesions on MRI. These patients were true familial genetic cases. Of the remaining 25% whose biological parents had a normal gradient echo MRI some were affected by a hereditary form of the disease as they were shown subsequently to carry a de novo mutation in one of the three CCM genes [Denier, Labauge et al, 2004], [Denier, Goutagny et al, 2004] and [Bergametti, 2005]. Whatever the cause, the real life implications of this are for the progeny of these people as well as themselves in terms of genetic counselling and screening. For researchers like myself gathering a cohort of apparently ‘sporadic’ cases it is sobering that, undoubtedly, a significant proportion of our multiple cases will have a heritable form of the disease.
The nature, frequency and natural history of intracranial cavernous malformations in adults and hence have consequences for their children and also, potentially, for their extended asymptomatic family.

1.2.2 Radiotherapy cavernomas

It was as recent as 1994 when it was first mooted [Gaensler, 1994] that intracranial cavernomas develop post radiotherapy. The effect is largely evident in children [Nimjee, 2006] although the much more rare de novo formation post radiotherapy in adults is also documented [Alexander, 1998] and [Furuse, 2005]. The three most common primary lesions requiring radiotherapy and subsequently leading to cavernoma development are medulloblastoma, glioma and acute lymphoblastic leukaemia in decreasing order of frequency [Nimjee, 2006]. There are wide ranges of latency periods published in case reports but bigger case series estimate a mean latency period of 8.9 years [Nimjee, 2006] to a median latency period of 10.5 years [Heckl, 2002] post radiotherapy treatment. What is clear from Heckl’s study is that the length of latency is directly related to the dose of radiation given [Heckl, 2002]. What is also clear from the literature is that cavernomas develop inside the radiation field and also the radiation port regions.

Why intracranial radiation should result in cavernoma formation is still unclear, as is the aetiology of sporadic intracranial cavernoma formation. One theory, however, supposes the involvement of vascular endothelial growth factor (vEGF) as a possible mechanism post radiotherapy inducing angiogenesis [Tsao, 1999]. This would tie in
The nature, frequency and natural history of intracranial cavernous malformations in adults with the potential mechanisms emerging in the literature about pathogenesis of familial and sporadic cavernomas i.e. abnormal angiogenesis. However, these are all theoretical at the moment and are some way from a cogent explanation of cavernoma pathogenesis. However, the reality is that cavernomas form in some people, particularly children, post radiotherapy to the brain and also spinal cord.

1.3 Radiological diagnosis of intracranial cavernous malformations

Cavernomas are low flow collections of vascular channels lined by endothelium and collagen but without any intervening brain parenchyma. As discussed previously (section 1.1.1) there is also an absence of the elastic and smooth muscle components of the ‘normal’ vessel walls. The caverns or vascular channels contain blood at various stages of stasis, thrombosis, organisation and calcification. Initially they were diagnosed on post mortem and thought to be vanishingly rare. Subsequently with the advent of cerebral angiography (1927) their existence was implied by displacement of the normal angioarchitecture but they were not directly visualised due to their low flow. They were conspicuous by their absence and hence the umbrella term ‘angiographically occult vascular malformations’. Again the frequency with which they were diagnosed was so low that their clinical significance in population terms was often doubted. Nor are they easily identified on CT imaging unless they are large and contain a substantial amount of calcification. Therefore, until the advent of MR imaging they remained largely under the clinical radar.
The nature, frequency and natural history of intracranial cavernous malformations in adults

In the mid 1980’s when MR was introduced into clinical use, clinicians began to realise the significance of cavernomas in terms of morbidity among patients and also, occasionally, mortality. Since then much has been published about the usefulness of imaging in the diagnosis of cavernomas, in particular asymptomatic lesions.

Pathology remains the established gold standard for diagnosis of intracranial cavernomas but, with the evolution of MR scanners and techniques, MR is fast assuming the upper hand in the diagnostic algorithm for cavernomas. It has distinct advantages over pathology in that it is non-invasive, can be done repeatedly in life and can be used without any harmful side effects. Therefore, it is crucial to get the imaging and pathological correlation right. In this section I will discuss the role imaging plays, firstly, in establishing the diagnosis and, secondly, in expanding the knowledge base about the aetiology and development of cavernomas.

1.3.1 Cerebral angiography

Cerebral angiography is a technique where catheter access to the cerebral arterial system is gained by direct puncture of, usually, the femoral artery. There is synchronous contrast injection directly into the arterial system with real time screening to observe the outlined cerebral vasculature. While the technique is a lot more refined today than when it was originally developed in Portugal in 1927 by Moniz, the principle is much the same. Prior to non-invasive imaging of the brain cerebral angiography was the only way of indirectly imaging intracranial...
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cavernomas. The clues to their presence were a paucity or displacement of the normal angioarchitecture of the brain on early arterial phase imaging without abnormal arterial feeding vessels, or displacement of vessels by mass effect from haemorrhage outside the cavernoma. On slightly delayed phase screening a subtle vascular blush is sometimes evident and in the venous phase a few large draining veins may be seen [Bartlett, 1977] & [Numaguchi, 1977]. The technique of prolonged injection of contrast helps delineate intracranial cavernomas [Rosenbaum, 1969]. Although angiography suggested the possible presence of intracranial cavernomas, it was by no means specific in the diagnosis of these ‘angiographically occult vascular malformations’ [Hallam, 1998] and it was not until the advent of computed tomography (CT) and MR in the 70’s and 80’s respectively that imaging could begin to rival pathology as the ‘gold standard’ for diagnosis of intracranial cavernomas.

1.3.2 Computed Tomography (CT) imaging

By the mid 1970’s and early 1980’s there was a body of evidence amassing that highlighted the usefulness of CT in combination with angiography in detecting intracranial cavernomas and sometimes in distinguishing them from the other subtypes of angiographically occult or low flow vascular malformations [Bartlett, 1977] and [Maehara, 1981]. The CT features are described as “round or oval hyperdense lesions without significant mass effect and with normal surrounding brain tissue in the majority of cases” [Sage, 1993]. They may also appear calcified...
The nature, frequency and natural history of intracranial cavernous malformations in adults and occasionally have a post contrast blush. Again, although these features suggest the diagnosis, they are not specific for cavernomas but indicative often of the more general category of ‘low flow’ lesions (cavernomas, partially thrombosed AVMs, venous angiomas and capillary telangiectases) [Rapacki, 1990] or granulomas, oligodendrogliomas, astrocytomas and thrombosed AVMs.

**1.3.3 Magnetic Resonance (MR) imaging**

By the mid to late 1980’s studies were being published comparing CT imaging and angiography to the utility of the newly introduced MR imaging in the diagnosis of pathologically verified cavernomas [Rigamonti, 1987] and [Harder, 1989]. It quickly became clear that MR was far superior in its sensitivity and also specificity although this was not rigorously quantified until our study, the details of which come later in the thesis (Chapter 8).

An illustration of the new clinical significance of MR in the correct diagnosis of intracranial cavernomas was highlighted by Preul et al [Preul, 1992]. 11 cases of brainstem cavernomas were misdiagnosed on CT and angiography as brainstem tumours. Patients had undergone a variety of treatments such as external radiation, ventriculo-peritoneal shunting, corticosteroid treatment and brainstem biopsy leading to a diagnosis of glioma. Subsequent MR scans depicted the characteristic appearance of intracranial cavernomas and 6 patients eventually underwent stereotactic radiosurgery.
A whole plethora of studies from the mid 1980’s and 1990’s have catalogued the superior utility of MR over CT [Vielvoye, 1992], [Biondi, 1986] and also the typical appearances of cavernomas on MR imaging [Barker, 1993], [Bien, 1986]. In 1994 however, Zabramski et al published the seminal study describing a classification system for intracranial cavernomas based on their MR signal characteristics and also their pathological characteristics [Zabramski, 1994]. This classification depicted in Table 1 is now in widespread use and has not yet been superseded by any other classification system in clinical practice.

### Table 1 Zabramski classification

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>MR signal characteristic</th>
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</table>
| **Type 1**  | T1\(^1\): hyperintense core  
|             | T2\(^2\): hyper- or hypointense core with surrounding hypointense rim  |
| **Type 2**  | T1: reticulated mixed signal core  
|             | T2: reticulated mixed signal core with surrounding hypointense rim  |
| **Type 3**  | T1: iso- or hypointense  
|             | T2: hypointense with a hypointense rim that magnifies the size of the lesion  
|             | GE\(^3\): hypointense with greater magnification than T2  |
| **Type 4**  | T1: poorly seen or not visualized at all  
|             | T2: poorly seen or not visualized at all  
|             | GE: punctate hypointense lesions  |

\(^1\) T1 weighted sequence on standard spin echo MRI  
\(^2\) T2 weighted sequence on standard spin echo MRI  
\(^3\) Gradient echo sequence
The nature, frequency and natural history of intracranial cavernous malformations in adults

Magnetic resonance imaging is developing year on year. As technology and our understanding of how it can translate into clinical use advances, the degree of sensitivity and specificity of MR in the diagnosis of cavernomas also improves. Fundamental to this is the understanding at a molecular level of the behaviour of different forms of iron within the brain such as ferritin and haemosiderin when placed within the magnetic field of an MR scanner [Vymazal, 2000] and thus as a consequence the characteristics intrinsic to cavernomas that specifically determine their appearance on different MR sequences.

Nearly twenty years after Zabramski defined the radiological subtypes of cavernomas, the increasing sophistication of MR imaging combined with our evolving understanding of the pathological basis underpinning what we see on images allows us to question the validity of Type 4 cavernomas as described by Zabramski. These punctate hypointense lesions seen only on GE MR sequences or SWI are made visible by the paramagnetic properties of blood products or calcification both of which are indeed associated with cavernomas but importantly this is identical to the appearance of microbleeds seen in conditions such as hypertensive encephalopathy and cerebral amyloid angiopathy. Clearly this category of cavernoma has overlap with other pathologies and must not be over relied upon.

1.3.3.1 T1 & T2 spin-echo and Fast spin-echo sequences

The early studies of MR were based on simple T1 & T2 weighted spin echo sequences [Barker, 1993], [Biondi, 1986], [Bien, 1986]. These allow depiction of the
characteristic appearances of Zabramski Type 1, 11 and 111 lesions (table 1) [Zabramski, 1994]. However type 4 lesions are usually not seen at all by using these sequences alone. T1 & T2 spin-echo are also still the mainstay of most general brain imaging protocols and are often the first sequences done even in the setting of cerebral haemorrhage or suspected vascular malformations.

1.3.3.2 T2*, T1 & T2 gradient echo sequences

These sequences focus particularly on accentuating the susceptibility effects of paramagnetic substances like haemosiderin, thus increasing the prominence of the rim of signal loss which characteristically surrounds type 1 to 3 cavernomas (this feature is more commonly known as ‘blooming artefact’). To be visualised at all, type 4 lesions rely on this *blooming artefact* and are therefore exclusively demonstrated on gradient echo sequences. Many small series have been published about the superiority of these sequences in diagnostic algorithms for intracranial cavernomas [Siebner, 1999], [Brunereau, 2000] & [Duchene, 2002]. Through these, albeit small studies, it has become clear that T2* gradient echo wins out in terms of maximising sensitivity and specificity of MR in the diagnosis of intracranial cavernomas. Once a cavernoma is suspected it now forms part of the MR protocol for diagnosis of intracranial cavernomas in most neuroscience centres. Because of time pressures on MR scanners in most NHS regions, however, gradient echo is still not a sequence used for routine screening of the brain.
1.3.3.3 Susceptibility weighted imaging (SWI)

This is an emerging high-resolution 3D-gradient echo sequence that creates an image based on T2*-contrast and the phase changes due to magnetic susceptibility. The magnetic susceptibility of deoxygenated blood, haemosiderin, methaemoglobin or ferritin produce a strong hypointense signal in the processed susceptibility weighted images and therefore allows high resolution depiction of venous structures, blood products and iron deposits. The technology has been available in clinical practice since 1997 [Reichenbach, 1997] but is rarely part of the routine imaging protocols for brain cavernomas. This is likely due to the prolonged acquisition times when using a 1.5tesla MR scanner. With higher field strength scanners (3 tesla and above) come improved conditions for SWI and as these scanners become more widespread in clinical practice, so too will the use of SWI. The major advantages of SWI is its superiority in detecting a greater number and smaller cavernomas as reported in several studies in the last 10 years [Rauscher, 2005],[Sehgal, 2005], [Lee, 1999], [Pinker, 2007] and [de Souza, 2008]. Also, several studies have reported the excellent depiction of developmental venous anomalies on non-contrast enhanced susceptibility weighted imaging over conventional MR imaging [Fushimi, 2008], [Lee, 1999], [Mittal, 2009] and [Tsui, 2009]. No published studies however report on the use of SWI in cavernoma cases associated with developmental venous anomalies although it is likely that its superiority will be demonstrated here also. This would have specific benefits in terms of pre-operative planning.
The major drawback of SWI is the prolonged acquisition time. However this can now be compensated for with higher field strength scanners. Once these are in widespread use in the clinical setting, this issue should cease to be a limiting factor. Signal dropout and phase artefacts, particularly at air-tissue interfaces, can impinge on the detection of cavernomas in particular areas such as the rostral skull base and the temporal lobe adjacent to the petrous bone. Another problem particularly relevant for size measurement and surgical planning is the more marked ‘blooming’ of strongly paramagnetic blood products, particularly at higher field strengths, thus artificially increasing lesion size. There are some technical ways of limiting the impact of this problem but details of this are beyond the scope of this thesis.

1.3.3.4 Diffusion tensor imaging (DTI) and tractography

This is a new potentially exciting adjunct to MR imaging that may give new insights into the effects of cavernomas on the adjacent white matter and how the haemosiderin and white matter affected by it survive their intimate relationship. Diffusion tensor (DT) imaging aids visualisation of the directionality and orientation of the white matter tracts of the brain. Recent studies have used DT tractography to characterise the haemosiderin rim surrounding the cavernoma and also as an aid in surgical planning for the resection of cavernomas in eloquent areas. Cauley et al [Cauley, 2010] performed tractography in 18 patients with solitary cavernomas and concluded that the central core of cavernomas deviate white matter tracts around them, with tracts often passing through the haemosiderin rim on their way. Data
The nature, frequency and natural history of intracranial cavernous malformations in adults

from this study also supported the idea that the haemosiderin rim is, at least in part, made up of viable tissue and is intimately associated with white matter tracts deviated around the central lesion. Chen et al reported that DT fibre tracking revealed the anatomical relationship between local eloquent tracts and the cavernoma, which altered their surgical approach to the brainstem and helped prevent patient morbidity[Chen, 2007] and [Chen, 2007] . Niizuma et al [Niizuma, 2006] report the successful use of fiber tracking to locate the displaced corticospinal tract for the removal of a paraventricular cavernoma. Therefore it appears that the future of DT imaging lies as a tool within the surgical planning process and also as an aid in deepening our understanding of the relationship between lesion location, size and clinical symptoms.

1.4 Role of MR imaging in establishing the natural history of cavernomas.

Moving on from my discussion on the role of imaging in the diagnosis of cavernomas, imaging has also played a significant role in dispelling the myth that cavernomas are congenital lesions. The spontaneous formation of de novo cavernomas in both the familial and sporadic forms is now well documented using MR imaging.

In 1994, Zabramski et al [Zabramski, 1994] performed serial MR scans on patients with familial cavernomas and documented the formation of six new lesions in 21 patients during an average follow-up period of 2.2 years. Similarly in 2000
Brunereau et al [Brunereau, 2000] retrospectively reviewed serial MR scans on patients with the familial form of the disease and again confirmed the formation of de novo lesions at a quoted rate of 0.2 lesions/patient-year with an average follow-up of 3.2 years. Similar de novo development has also been documented in the sporadic form of the disease [Pozzati, 1989] and [Detwiler, 1997]. In my cohort at least one patient’s sequential MR imaging identified development of a second cavernoma during the period of observation. The clear formation of new lesions, along with the knowledge that the KRIT 1 protein acts as a tumour-suppressor gene, makes a case for the reclassification of cavernomas as benign vascular tumours, similar to haemangiomas, rather than congenital lesions. This has implications for the calculation of bleeding risks as it can no longer be assumed that the at risk period is from birth. Serial MR also demonstrates that cavernomas, whether familial or sporadic, are not static lesions. Their size can increase over time without direct evidence of haemorrhage [Zabramski, 1994], [Pozzati, 1989] and [Pozzati, 1996].

Finally, serial MR imaging has also allowed the connection between radiotherapy and subsequent development of cavernomas to be made [Nimjee, 2006], [Pozzati, 1996] and [Larson, 1998]. This de novo formation post radiotherapy treatment has a latent period of 3 to 10 years. These new insights into cavernoma development and behaviour captured by MR imaging add to the evolving body of evidence regarding their aetiology and natural history.
1.5 In summary

- Approximately 110,000 people are diagnosed each year in England with stroke.

- Intracranial cavernous malformations are a rare cause of stroke, most significant in young people.

- Histopathology is the Gold standard for diagnosis but MR imaging is now accepted as a close second which is more clinically useful.

- A proportion of cavernomas coexist with developmental venous anomalies.

- Intracranial CMs can be familial, sporadic or secondary to radiotherapy.

- The conventional wisdom that CMs were present from birth is now known to be false. They appear de novo at various points throughout life.
Chapter 2:

Aims and outline of thesis
2.1 Introduction

The ambition of this thesis is to improve the accuracy and power of aspects of intracranial cavernous malformation epidemiology already published [Al-Shahi, 2003] and then to present new high quality data about their natural history, in particular presentation and prognosis.

The natural history of any disease is composed of certain stages which are graphically illustrated below:

**Figure 4 Graphic illustration of the stages of natural history of a disease**
[Sackett's Clinical Epidemiology, 1991]

<table>
<thead>
<tr>
<th>Biologic onset</th>
<th>Early diagnosis possible</th>
<th>Usual clinical diagnosis</th>
<th>Outcome</th>
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Time

In the context of intracranial cavernous malformations, biologic onset is unknown, except to say they are not present at birth. The usual clinical diagnosis is made when a patient presents with symptoms. But, now that MR imaging is widely available, early asymptomatic diagnosis is becoming increasingly more common. It is really
The nature, frequency and natural history of intracranial cavernous malformations in adults

from this point that the story of cavernoma natural history begins in practice and so too in this thesis.

2.2 Specific aims of thesis

2.2.1 Incidence of intracranial cavernous malformations in SIVMS

Incidence is a measure of the risk of developing a new condition within a specified period of time. A preliminary review of the literature on cavernomas clearly indicated a dearth of studies that meet the criteria for the proper measurement of incidence. The setting up of the first prospective, population-based study, SIVMS (The Scottish Intracranial Vascular Malformation Study), in 1998 provided the patients to answer this key question.

2.2.2 Presentation and early prognosis of intracranial cavernous malformations in SIVMS

In terms of natural history, the logical step after estimation of disease incidence in a population-based cohort is to establish the modes of presentation and prognosis of the disease. Intracranial cavernomas are well documented as causes of haemorrhage, epilepsy, focal neurological deficits and many more neurological symptoms. What is not clear however, is the relative proportions with which these symptoms occur, and also how many cavernomas are asymptomatic at presentation? This information is
The nature, frequency and natural history of intracranial cavernous malformations in adults fundamental to understanding the condition and eventually uncovering patients’ true prognosis. SIVMS recorded modes of presentation and prognosis for a five year period (from January 1999 to December 2003) in an inception cohort, and as a prospective study of the Scottish population aged over sixteen years, is ideally designed to do this.

2.2.3 Treatment of intracranial cavernous malformations in SIVMS

The treatments available for cavernomas are complete or partial surgical excision, radiosurgery (Linear accelerator (LINAC) or Gamma-knife) or medical management of symptoms. Appropriate evaluation of treatments would ideally be in the form of a randomized controlled trial. For many reasons this is not currently feasible and unlikely to happen for many years to come. SIVMS is an observational study. All management decisions were taken remote to SIVMS and were between the clinician and patient. As a result, and compounded by the small numbers involved, I will merely describe the numbers that were treated and how they were treated, but drawing conclusions from these data would be ill advised and will not be done.

2.2.4 Validity of MR imaging in the diagnosis of cavernomas

As discussed already in Chapter 1 MR imaging has evolved as the most clinically appropriate diagnostic tool for intracranial cavernomas. It is also widely accepted to be the new ‘Gold standard’ in diagnosis and is even used in practice as a screening tool for relatives of patients with the familial form of the disease. However this
The nature, frequency and natural history of intracranial cavernous malformations in adults wisdom has never been objectively challenged in the literature and we set out to do this with a study designed to quantify the sensitivity and specificity of MR imaging in this setting. Validating the use of MR as a diagnostic tool for cavernomas was even more important for us as the criteria for inclusion in SIVMS were based on a definite diagnosis on MR imaging or histopathology. In practice, the vast majority of patients in SIVMS met the criteria for inclusion based solely on imaging.

2.3 Thesis structure

This thesis is structured as follows; the introduction, aims and outline are followed by a systematic review of the published literature on the natural history of intracranial cavernous malformations in adults. This will then be followed by a series of chapters focussing on the methods and results in SIVMS, a separate chapter for each of these topics; incidence, presentation, early prognosis and treatment. After this a separate chapter focussing on the validity of MR imaging in the diagnosis of cavernomas will round off results. The thesis will finally draw to a close with a conclusion and discussion about the future of research on brain cavernomas.

2.4 In summary

In summary, my aim was to establish the epidemiology and natural history of intracranial cavernomas in adults and also to quantify the suitability of MR imaging in their diagnosis. SIVMS was an excellent vehicle to do this.
Chapter 3:

A systematic review of the literature on intracranial cavernous malformations
3.1 Introduction

Embarking on a study and a thesis of this nature it is essential to familiarize oneself with the available literature relevant to the subject. Therefore I did an electronic search of the literature deliberately casting a wide net in my search strategy to err on the side of being over inclusive rather than under inclusive. My search strategy was devised with the help of Brenda Thomas, the Trials Search Co-ordinator of the Cochrane Stroke Group Editorial Team and my thanks go to her. The strategy was also reviewed by Dr Al-Shahi who at this point had amassed experience in exhaustive electronic searching of the literature.

The results of this search were the basis for the literature review in this chapter. It was last updated in April 2011 when my thesis began taking form.

3.2 Methods

The 20 line search strategy devised (see tables 2 & 3) was used to electronically search the Ovid MEDLINE and EMBASE databases. My search was not limited by language, patient’s age or study type. As such any paper whether case report or randomized controlled trial was retrieved. MEDLINE was searched from 1966 to April 2011 and EMBASE from 1980 to April 2011. They yielded respectively 2137 and 3167 references which were imported into reference manager software version 10.0. A duplicate search was performed and any duplicates were deleted. 3038 references remained. The titles and abstracts of all references were reviewed and
The nature, frequency and natural history of intracranial cavernous malformations in adults coded with personalised keywords such as 'incidence, prognosis, presentation etc'.

For the review of studies of incidence, for example, all abstracts coded as such were retrieved and the full articles of all except case reports reviewed. The electronic search was supplemented by a hand search of the bibliographies of pertinent articles. This process was followed for studies of presentation, prognosis and treatment.

I separately searched for completed and ongoing clinical trials with any connection to cerebral cavernous malformations. This search encompassed The Cochrane Library including the Cochrane Stroke Group’s specialised register of trials (http://www.thecochranelibrary.com/ and http://stroke.cochrane.org/) and also the US National Institute of Health’s’ clinical trials registers (http://clinicaltrials.gov/ and http://www.strokecenter.org/trials/). This produced no results.
The nature, frequency and natural history of intracranial cavernous malformations in adults

Table 2 Electronic literature search strategy; Ovid Medline from 1966 to April 2011

<table>
<thead>
<tr>
<th>Line</th>
<th>Search term</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Exp Cerebral arteries/</td>
</tr>
<tr>
<td>2</td>
<td>expCerebral arterial diseases</td>
</tr>
<tr>
<td>3</td>
<td>Exp Cerebral veins/</td>
</tr>
<tr>
<td>4</td>
<td>(cerebral or cerebell$ or brain$ or supratentorial or infratentorial</td>
</tr>
<tr>
<td>5</td>
<td>Exp Hemangioma, cavernous/</td>
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<tr>
<td>6</td>
<td>Cavernous haemangioma$.tw</td>
</tr>
<tr>
<td>7</td>
<td>Cavernoma$.tw.</td>
</tr>
<tr>
<td>8</td>
<td>Cavernous angioma$.tw</td>
</tr>
<tr>
<td>9</td>
<td>(cavernous adj5 malformation$).tw</td>
</tr>
<tr>
<td>10</td>
<td>Exp Intracranial arteriovenous malformations/</td>
</tr>
<tr>
<td>11</td>
<td>Exp cerebral haemorrhage/</td>
</tr>
<tr>
<td>12</td>
<td>Exp epilepsy/</td>
</tr>
<tr>
<td>13</td>
<td>Exp cerebral angiography/</td>
</tr>
<tr>
<td>14</td>
<td>Exp brain neoplasma/ or exp infratentorial neoplasms/ or exp</td>
</tr>
<tr>
<td>15</td>
<td>1 or 2 or 3 or 4</td>
</tr>
<tr>
<td>16</td>
<td>5 or 6 or 7 or 8 or 9</td>
</tr>
<tr>
<td>17</td>
<td>10 or 11 or 12 or 13 or 14</td>
</tr>
<tr>
<td>18</td>
<td>15 and 16</td>
</tr>
<tr>
<td>19</td>
<td>5 and 17</td>
</tr>
<tr>
<td>20</td>
<td>Exp Hemangioma, cavernous, central nervous system/</td>
</tr>
<tr>
<td>21</td>
<td>18 or 19 or 20</td>
</tr>
</tbody>
</table>
The nature, frequency and natural history of intracranial cavernous malformations in adults

### Table 3 Electronic literature search strategy; Embase from 1980 to April 2011

<table>
<thead>
<tr>
<th>Set</th>
<th>Search</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exp brain artery/</td>
</tr>
<tr>
<td>2</td>
<td>Exp brain vein/</td>
</tr>
<tr>
<td>3</td>
<td>(cerebral or cerebell$ or brain$ or supratentorial or infratentorial or parenchymal).tw.</td>
</tr>
<tr>
<td>4</td>
<td>Exp Cavernous Hemangioma/</td>
</tr>
<tr>
<td>5</td>
<td>Cavernous haemangioma$.tw</td>
</tr>
<tr>
<td>6</td>
<td>Cavernoma$.tw.</td>
</tr>
<tr>
<td>7</td>
<td>Cavernous angioma$.tw</td>
</tr>
<tr>
<td>8</td>
<td>(cavernous adj5 malformation$).tw</td>
</tr>
<tr>
<td>9</td>
<td>Exp Brain arteriovenous malformation/</td>
</tr>
<tr>
<td>10</td>
<td>Exp Brain haemorrhage/</td>
</tr>
<tr>
<td>11</td>
<td>Exp epilepsy/</td>
</tr>
<tr>
<td>12</td>
<td>Exp brain angiography/</td>
</tr>
<tr>
<td>13</td>
<td>Exp brain hemangioma/ or exp brain stem tumour/ or exp brain tumour/ or exp cerebellum tumour/ or exp intracranial tumour/</td>
</tr>
<tr>
<td>14</td>
<td>1 or 2 or 3</td>
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<td>9 or 10 or 11 or 12 or 13</td>
</tr>
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<td>17</td>
<td>14 and 15</td>
</tr>
<tr>
<td>18</td>
<td>4 and 16</td>
</tr>
<tr>
<td>19</td>
<td>17 or 18</td>
</tr>
</tbody>
</table>
3.3 Incidence / Measurement of disease occurrence

Measurement of disease occurrence (incidence/prevalence) is fundamental to the science of disease epidemiology. Although the concept is simple the practical application of theoretical incidence measurement is complex. Virtually all studies of incidence have inherent weaknesses and execution of the perfect study of disease incidence is almost impossible in today’s world with regard to financial and ethical constraints – not that I am denouncing these constraints, I am simply highlighting the implications that they have for clinical research.

Estimation of disease incidence, or indeed prevalence, is essential for two main reasons. Firstly, it is the cornerstone of health service planning and allows health service delivery organisations to ‘prioritise for action’ and secondly, but by no means least, it is the inaugural step in establishing the natural history of any disease process. I will now discuss the definition of incidence and the methodological criteria that are desirable in a study of incidence.

Incidence is loosely defined as the counting of new cases in a defined population at risk. More commonly there is a dimension of time added to it and consequently the conversion of absolute numbers into a ‘rate’ has much more use, as was demonstrated by Snow in the London cholera epidemic in 1855. There are two main ways of calculating incidence rate. Firstly, true ‘incidence rate’ is what Last calls “person-time incidence rate”[Last, 2001]. Each person in the study population
The nature, frequency and natural history of intracranial cavernous malformations in adults contributes one person year to the denominator for each year of observation before disease develops or that person is lost to follow-up. The numerator refers strictly to first events of disease. The units of rate always include a dimension of time.

The second, and probably the one most relevant to this clinical setting, is the cumulative incidence rate or crude incidence. It is a simpler measure of the occurrence of disease. Unlike incidence rate, it measures the denominator only at the beginning of the study. The denominator is therefore the number of people free of the disease in the population at risk at the beginning of the study. It is often presented as the rate per 100,000 population per year.

Germane to the practice of disease quantification in a population is the ability to diagnose the disease in question definitively. In the specific setting of this thesis diagnosis of intracranial cavernomas is well established on histopathological grounds and now also on imaging since the advent of MR scanners [Zabramski, 1994] as discussed in Chapter 1. Either mode of diagnosis would be appropriate for use in a clinical research setting but the non-invasive imaging method has many obvious advantages.

As intracranial cavernomas can and do arise sporadically in the general population, a study population must therefore include the entire population or a representative sample. Hospital or single centre based studies are suboptimal because of the many
The nature, frequency and natural history of intracranial cavernous malformations in adults

selection biases to which they are subject. In general they ignore cases that are either too mild or too severe (e.g. sudden death) to require hospitalisation.

To minimise the many biases and confounding factors to which observational research is vulnerable, data and case collection should be prospective. Retrospective data collection is unreliable and specifically subject to reporting bias and, therefore, should generally be avoided.

As previously discussed it is well documented that intracranial cavernomas can develop at any point in life (section 1.2.1) i.e. they are not congenital lesions. The specific point in time at which they develop (biologic onset) is all but impossible to determine as many will be asymptomatic for an indefinite period. Diagnosis of asymptomatic cases is serendipitous unless an entire population was screened with MR imaging at regular intervals. This would be an impossible task for many reasons and therefore many studies make attempts within their methodological limitations to estimate the occurrence of asymptomatic cavernomas. With this in mind complete case ascertainment is the unattainable goal of any study of cavernoma incidence but some studies get closer than others to estimating it correctly.

3.3.2 Incidence of cavernomas in the literature

Once I applied the desired criteria for a study of incidence [Sudlow, 1996] (table 4) to the non-case report studies retrieved in the literature search I soon realized that no
The nature, frequency and natural history of intracranial cavernous malformations in adults study met more than two out of four criteria and all had serious methodological flaws (table 5). Therefore, for the purposes of this review I arbitrarily decided to analyze all large studies in terms of their usefulness and problems (number of cases (n) = 206 was the smallest study included).

Table 4 Desired criteria for studies of incidence

- Definite diagnosis, using standard and explicit criteria
- Population based
- Prospective
- Complete case ascertainment (symptomatic and, if possible and appropriate, asymptomatic)
The nature, frequency and natural history of intracranial cavernous malformations in adults

Table 5 Large studies of cavernoma incidence

<table>
<thead>
<tr>
<th></th>
<th>Population based</th>
<th>Prospective case ascertainment</th>
<th>Complete case ascertainment</th>
<th>Definite diagnosis</th>
<th>*N&gt;1000</th>
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<tr>
<td><strong>Autopsy series</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Berry, 1966</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
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<tr>
<td>McCormick, 1966</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
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<tr>
<td>Jellinger, 1986</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Otten, 1989</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td><strong>MRI series</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del Curling, 1991</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Robinson, 1991</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Katzman, 1999</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Weber, 2005</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Vernooij, 2007</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Hartwigsen, 2010</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>●</td>
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</tr>
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<td><strong>Population based series</strong></td>
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<tr>
<td>Brown, 1996</td>
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<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Mathieson, 2003</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

*N = number of cases

There was only one truly population-based study of incidence [Brown, 1996] in the literature (Table 5). It is based on the Rochester Epidemiology Project Medical Records Linkage System. This study was not issue free however. It was retrospective thus making it susceptible to reporting bias. Diagnostic techniques were primitive.
The nature, frequency and natural history of intracranial cavernous malformations in adults during this study period (1965 – 1992) and interestingly no cavernomas were diagnosed prior to 1985, when MR imaging was first introduced. This suggests that many asymptomatic and symptomatic cavernomas went undetected as diagnostic techniques were not sufficiently refined to pick up the diagnosis when a cavernoma was present. Also, as MR imaging was not available, the main mode of diagnosis was on autopsy and, as cavernomas are less likely than AVMs to cause fatal haemorrhage, the chances of picking them up on post mortem alone is slim – one cavernoma was found with this method in Brown’s study spanning 27 years. The age and sex adjusted detection rates for all cavernomas were estimated to be somewhere between 0.17 and 0.5 per 100,000 per year.

There was a second study that claimed to be population based [Mathieson, 2003] (Table 5). This was a Swedish single centre study based at a neurosurgical centre. The claim was that, in Sweden, the medical records system is such that any patients from their population, but seen in another area, would have been notified to them and hence this allowed collection of all cases that come to light clinically. Based on this fact their retrospective estimation of symptomatic case incidence was 0.32 persons per 100,000 per year. All their asymptomatic cases were from imaging done on people who presented with unrelated head trauma, incidental spinal disease or studies done on controls from research studies. None were from autopsies. This makes their estimation of asymptomatic incidence at 0.08 persons per 100,000 per year likely to be an underestimate.
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The remainder of the large studies of frequency can be divided into two groups based on the source of cases – autopsy or MR imaging series. The autopsy series [Berry, 1966], [McCormick, 1966], [Jellinger, 1986] and [Otten, 1989] were predominantly single centre, retrospective studies reporting incidences, or more correctly prevalences, ranging from 0.02 to 0.53%. The cohorts were subject to much selection bias, reporting and recall bias. Thus it was likely that the very mild and also very severe cases such as sudden deaths in the community were not included as they never present to hospitals. Autopsy rates will also vary significantly from region to region depending on local policies. The studies were quite different in their settings and, therefore, comparison of populations between studies is quite hopeless.

Similarly, the studies of MR imaging series [Del Curling, 1991], [Robinson, 1991], [Katzman, 1999], [Weber, 2006], [Vernooij, 2007] and [Hartwigsen, 2010] are largely plagued by selection bias, reporting and recall bias although the most recent studies are getting closer to approximating the incidence of asymptomatic/incidental cavernomas. Their case incidences ranged from 0.12 to 0.9%, a wide range reflecting the varied study designs, access to and use of MR facilities in different geographic locations. The study by Vernooij in 2007 was embedded within the Rotterdam Prospective Population based Study and there was MR screening of eligible participants all aged >45yrs using a standardized protocol. This study is the one most likely to approximate to an ideal study of incidence although it excludes those under the age of 45yrs, and in any event, it is in fact a study of prevalence rather than incidence. The rates quoted in the study were a combination of prevalent cases with
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an existing cavernoma at the beginning of the study and incident cases who
developed a cavernoma during the study. The true split between these two groups in
the cohort is impossible to know as diagnosis was only made if the lesion was
present on MR imaging on one occasion. Therefore this was actually a study of
period prevalence i.e. those cases that were present on imaging during the duration of
the study. If all patients had been scanned on a particular day, for instance at the end
of the study, then this would have represented a point prevalence.

In the MR imaging series studies were again subject to selection bias in being
hospital/single centre based. Whole swathes of the population were excluded from
the studies and the cohorts were over selected.

In conclusion, the literature published on incidence/prevalence of intracranial
cavernous malformations is of poor methodological quality and/or hampered by
limited tools of diagnosis when the studies were performed prior to the widespread
availability of MR imaging.

Mindful of these complex issues SIVMS was designed as a practical, if imperfect
solution to the dearth of information available on the incidence and natural history of
intracranial cavernous malformations in adults. For reasons I will discuss later in the
thesis SIVMS is a study that stands methodologically apart from any in the literature
to date.
3.4 Presentation of intracranial cavernomas in the literature

How cavernomas present is important to consider, especially as our understanding of this has changed over the years. The symptomatic presentation of cavernomas has been clinically subdivided in the literature into four categories:

- Haemorrhage
- Focal neurological deficit
- Seizures
- Headache

The occurrence of asymptomatic cavernomas was thought to be rather small prior to MR imaging but what has become clear over the past twenty years is that the size of this group is growing fast with a reported prevalence in one study of 0.4% [Del Curling, 1991]. As you will see later in this thesis, this group is now the largest subtype of presentation in our population-based study, SIVMS. This raises all sorts of important questions about the significance of ‘incidental’ cavernomas. This, however, is a discussion not confined to cavernous malformations. Today there are many ‘incidental’ findings on MR imaging as the systematic review by Morris et al highlighted in the BMJ in 2009 [Morris, 2009]. This is fast becoming a real conundrum for clinicians. How significant are they? Who should we tell? What treatments can we offer? The answers are not clear.
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As a relatively poorly studied subgroup, this asymptomatic group have the potential to alter significantly our understanding of natural history to date. This possibility was clear early on in my review of the literature.

The literature published in peer reviewed journals touching on the subject of natural history or presentation of sporadic intracranial cavernous malformations consisted of data collected in all instances from a single centre, most commonly a surgical centre. There was no population-based data on the proportions of the subtypes of cavernoma presentation in a population.

All studies agreed on the subdivision of presentation into the five categories of: haemorrhage, focal neurological deficit, seizures, headache and incidental/asymptomatic. Comparison between cohorts was fruitless as the proportion of patients with each presentation subtype varied widely across the studies. Among studies with over 100 cases the breakdown of presentation subtype in the cohorts varied as shown in table 6 [Del Curling, 1991], [Barker, 2001], [Aiba, 1995] & [Porter, 1997]. As the cohorts originated mostly from single surgical centres, it is likely the variation was due to differences in referral practices between regions and countries. For example: sometimes only the most severely afflicted patients were referred to the centres for tertiary treatment and this may be the reason for a heavy preponderance of haemorrhagic and epilepsy presentations in these cohorts.
The nature, frequency and natural history of intracranial cavernous malformations in adults

Table 6 Published presentation subtypes

<table>
<thead>
<tr>
<th>Presentation subtype</th>
<th>Range of published estimates of the relative proportion of presentation subtypes within cohorts of natural history studies with n &gt; 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental</td>
<td>0 – 21 %</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>9 – 100%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0 – 50%</td>
</tr>
<tr>
<td>Focal neurological deficit</td>
<td>0 – 22%</td>
</tr>
<tr>
<td>Headache</td>
<td>0 – 34%</td>
</tr>
</tbody>
</table>

The cohort sizes varied enormously, from 13 [Tagle, 1986] to 141 [Barker, 2001] which is important to acknowledge. On occasion the cohort numbers in a publication were also bolstered by cases (case reports and small case series) already published in the literature. This practice serves to add to the description of types of presentation but falls far short of adding to our understanding of the burden of different types of presentation in a population.

In the literature, the focus on symptomatic cavernomas was to the exclusion of data on asymptomatic cases. Just three studies acknowledged inclusion of incidental, or more appropriately asymptomatic, cases, the largest being Aiba’a study with 23 incidentally diagnosed patients [Kupersmith, 2001], [Aiba, 1995] & [Sage, 1993].
Data collection was also most commonly retrospective. In fact Kondziolka’s study in 1995 was the only one to claim some prospective data collection [Kondziolka, 1995]. With retrospective selection of cases at surgical centres on the whole, it is difficult to imagine how asymptomatic cases could have come to light for inclusion and this is perhaps why they have not been on the whole.

Another issue highlighted by my review was the lack of clarity or consensus in the literature on the definitions of the different subtypes of presentation, especially concerning haemorrhage. This is a theme that also runs through the studies of prognosis. An example of the confusion is that some studies were content defining haemorrhagic presentation by imaging alone [Kondziolka, 1995] & [Kim, 1997], some combined imaging evidence with clinical symptoms [Aiba, 1995] and others were content with haemorrhage defined solely as clinical deterioration [Barker, 2001]. One study failed to document a clear definition of haemorrhage at all [Kim, 1997]. To cause even more obfuscation there was variation even within the definition of imaging evidence of haemorrhage – CT or MRI evidence, haemorrhage within or outside the lesion, and a minimum increase in size of the lesion before haemorrhage could be confirmed. This issue has been addressed recently in a workshop of the Angioma Alliance Scientific Advisory Board and a standardized definition of haemorrhage and other major outcomes has now been proposed [Al-Shahi, 2008].
Although epilepsy seems to be one of the major modes of presentation, the studies included in this review omit a clear definition of this clinical event also. Therefore the quantification of ‘epilepsy’ as a mode of presentation, and indeed as an outcome, is of limited use clinically. Lack of clarity limits the translation of ‘epilepsy rates’ onto other populations and also limits meta-analysis between studies. Refining epilepsy presentation definition, and similarly outcome definition, into categories such as; first ever seizure or epilepsy (meaning two or more seizures) but both referable to the anatomic location of the CM and not caused by another event such as haemorrhage, would be more useful.

As I will discuss later in this thesis, focal neurological deficit (FND), as a clinical event related to cavernomas can be defined in various ways. In an ideal world FND is symptoms or signs of neurologic dysfunction, referable to the anatomic location of the CM, but without evidence of ICH, cerebral infarction, epileptic seizure (Todd’s paresis), or migraine. To be precise about this in a research study setting would require all patients’ presenting with such symptoms to have prompt neurological evaluation combined with appropriate imaging. Unfortunately this is not always the case and therefore the overlap in terms of signs and symptoms between haemorrhage and FND as clinical events can be difficult to unpick. Studies thus far have failed to be explicit about their definitions of FND and therefore it is impossible to estimate how much overlap there is in these studies between the FND and haemorrhagic presentation groups.
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Headache will always be a contentious issue. The neurological community continues to be divided about whether cavernomas themselves, without overt haemorrhage, can cause headache by virtue of their anatomic location. In studies of presentation, and similarly studies of prognosis, I think it is reasonable to include it as a mode of presentation or outcome, but going one step further and ascribing a cause to it is less easy.

All of these issues play their part in undermining the quality of the available published data on the natural history and, more specifically, the frequency of the subtypes of presentation of intracranial cavernomas in a population. This was what SIVMS sought to address in the prospective, population-based design of the study with clear definitions of all clinical events.

3.5 Prognosis in the literature

3.5.1 Introduction

This particular aspect of the literature review was undertaken by me and Dr Al-Shahi. I formulated the search strategy as previously described and coded the search results accordingly. The inclusion criteria for studies of prognosis detailed in the next section were agreed between me and Dr Al-Shahi. Once I had done a preliminary sort through the published literature, the potentially relevant articles were read in full by both me and him. We independently decided which studies met our criteria for
The nature, frequency and natural history of intracranial cavernous malformations in adults inclusion and if disagreements arose, the final nine included in this review were as a result of consensus between us both.

3.5.2 Results

Once the diagnosis has been made and the patient has ‘presented’ we move into a subsection of the natural history called ‘clinical course’. In Sackett et al.’s book of Clinical Epidemiology there is a very eloquent description of the desired criteria of a study of clinical course/prognosis [Sackett’s Clinical Epidemiology, Chapter 6]. With good reason studies of prognosis should have the following criteria:

- Inception cohort – that is patients included at an early and uniform point
- Population based
- Complete follow-up achieved
- Explicit and objective terms used as prognostic outcomes
- Outcome assessment blinded to any potential prognostic factors

With the above in mind I reviewed the published literature.

No study met all of the desired criteria of a study of prognosis. Since various criteria were missing from all the studies reviewed I arbitrarily set my inclusion threshold to a cohort size of >50 cases and, therefore, distilled the published studies down to 9 of the more significant ones. These 9 also allow me to highlight the problems to date in the quality of published evidence regarding prognosis of intracranial cavernomas (table 7).
Table 7 Included studies of prognosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic certainty</th>
<th>Inception cohort</th>
<th>Prospective data collection</th>
<th>Population based</th>
<th>N&gt;5</th>
<th>Objective outcomes</th>
<th>Length of F/U</th>
<th>F/U complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson 1991</td>
<td>MRI &amp;/or pathology</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>66</td>
<td>Overt haem</td>
<td>26/12</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aiba 1995</td>
<td>MRI &amp;/or pathology</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>110</td>
<td>Haem rate</td>
<td>Haem=4.2yrs</td>
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<td></td>
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<td></td>
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<td>Disability</td>
<td>Seizure=7.9yr</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>outcome</td>
<td>Incidental=2.3yrs</td>
<td></td>
</tr>
<tr>
<td>Kondziolk a 1995</td>
<td>CT &amp;/or MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>122</td>
<td>Haem rate</td>
<td>34/12</td>
<td>75%</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Seizure rate</td>
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</tr>
<tr>
<td>Porter 1997</td>
<td>MRI &amp;/or pathology</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td></td>
<td></td>
<td></td>
<td>Haem rate</td>
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</tr>
<tr>
<td>Kim 1997</td>
<td>MRI &amp;/or pathology</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>62</td>
<td>Haem rate</td>
<td>22.4/12</td>
<td>??</td>
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<td>Signal changes</td>
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<td></td>
<td></td>
<td></td>
<td>over time</td>
<td></td>
<td></td>
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<tr>
<td>Abdulrauf 1999</td>
<td>MRI &amp;/or pathology</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>55</td>
<td>Haem rate in CMs</td>
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</tr>
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<td></td>
<td>v’s CM +VMs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moriarty 1999</td>
<td>MRI &amp;/or pathology</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>68</td>
<td>Haem rate</td>
<td>5.2yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>seizure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barker 2001</td>
<td>CT/MRI/ANGIO &amp;/or Pathology</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>141</td>
<td>Haem rate over</td>
<td>3.8yrs</td>
<td>?100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>time after first</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantu 2005</td>
<td>MRI</td>
<td>yes</td>
<td>yes</td>
<td>No</td>
<td>133</td>
<td>Haem rate</td>
<td>5yrs</td>
<td>92%</td>
</tr>
</tbody>
</table>

A systematic review of the literature on intracranial cavernous malformations
At this point, I must highlight that I will deal firstly with untreated prognosis. I will look separately at the treatments available and outcomes post treatment.

Diagnostic certainty and cohort size >50 were the only features of the studies where they all met with my desired standard. Beyond that there was uniform failure of any study to be population based. All were based in single, mostly tertiary, referral centres. This introduces a variety of potential biases such as centripetal, popularity, referral filter and diagnostic access biases. All have the same effect—potentially generating patient samples that are much different from those found in the general population. The likelihood in this setting is that the cases being referred, very often for treatment, would be more severe than those found generally in the population. Any conclusions drawn on a cohort like this would overestimate the pessimism of prognosis of that disease.

Assembly of an inception cohort (inclusion at an early and uniform point of the disease) is key in a study of clinical course and prognosis. Failure to do this can have an unpredictable effect on the results. If focusing only on those who are at the severe end of the spectrum and being referred for any potential treatments, the likelihood is that the milder cases who never reach tertiary neurosurgical centres will not be taken into consideration and the prognosis will seem gloomier than the reality. It can also have the opposite effect however. Supposing there are many patients who are
The nature, frequency and natural history of intracranial cavernous malformations in adults

severely disabled at presentation and considered unsuitable for referral to a
neurosurgical centre, or even those who die at presentation never getting to the
tertiary centres, then the opposite can occur. Those being referred on for treatment
may be a select group who have survived the worst and are likely to do better
anyway.

Objective outcomes and prospective data collection are interlinked. For the person(s)
deciding on the presence or absence of a particular outcome, clear unambiguous
definitions should exist and preferably they should be blinded to any potential
prognostic factors of importance. As human beings we are susceptible to a greater or
lesser degree to expectation and diagnostic-suspicion biases but good methodological
practices should minimize these effects. Also, having clear uniform definitions of
outcomes in use across the literature should make it easier to compare and combine
studies leading to greater powered results. This is the aspiration of the Angioma
Alliance Scientific Advisory Board when they tackled the definition of haemorrhage
in 2008 [Al-Shahi, 2008].

Completeness of follow-up cannot be over emphasised. All members of the inception
cohort should be accounted for at the end of the follow-up period as patients do not
disappear from a study for trivial reasons – they recover, die, move away or get fed
up but all of these situations influence prognosis.
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As evident from table 7 there is no perfect study of prognosis and with all the varying flaws, this is probably why, for example, results of haemorrhage rates vary so very widely between studies (table 8).
The nature, frequency and natural history of intracranial cavernous malformations in adults

Table 7 Haemorrhage rates and definitions in major studies of prognosis

<table>
<thead>
<tr>
<th>Haemorrhage rate</th>
<th>N</th>
<th>Details of rates</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Robinson 1991</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. 0.7% per year per lesion</td>
<td>66</td>
<td>I. 1 bleed in follow up of 143 lesion years</td>
<td>I. Retrospectively ascertained.</td>
</tr>
<tr>
<td><strong>Alba 1995</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. 0.39% per year</td>
<td>110</td>
<td>I. 1 case in 254 yrs of follow up</td>
<td>I. 1st bleed in pts presenting with epilepsy based on the follow-up period</td>
</tr>
<tr>
<td>II. 22.9% per year per lesion</td>
<td></td>
<td>II. 26 lesions out of 62 lesions caused 45 bleeds over a mean of 3.12 years of follow up</td>
<td>II. Re-bleed rates per lesion in pts presenting with haemorrhage over a follow-up period of 3.12yrs</td>
</tr>
<tr>
<td>III. 1.5% per year</td>
<td></td>
<td>III. 4 pts out of 62 pts over 262 patient years of follow up</td>
<td></td>
</tr>
<tr>
<td><strong>Kondziolka 1995</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. 1.3% per year</td>
<td>122</td>
<td>I. 61 haemorrhages in 122 patients in 450.6 patient years</td>
<td>I. Retrospective haemorrhage rate assuming lesions present from birth &amp; counting one bleed per patient</td>
</tr>
<tr>
<td>II. 2.63% per year</td>
<td></td>
<td>II. 9 bleeds in 341.6 patient years of follow up</td>
<td>II. Prospective bleed rate based only on the prospective follow-up period &amp; counting multiple bleeds per patient</td>
</tr>
<tr>
<td>III. 0.6% per year</td>
<td></td>
<td>III. 1 bleed out of 61 pts but no clear info on length of follow up</td>
<td>III. Bleed rates in those without prior haemorrhage (other presentation)</td>
</tr>
<tr>
<td>IV. 4.5% per year</td>
<td></td>
<td>IV. 8 bleeds in 7 pts and no clear info on the period of follow up</td>
<td>IV. Bleed rate in those with a prior haemorrhage</td>
</tr>
<tr>
<td><strong>Porter 1997</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. 1.6% per year</td>
<td>173</td>
<td>I. 7 bleeds in 110 pts with 427 patient/years of follow-up</td>
<td>I. Overall annual rate of bleeding during follow-up</td>
</tr>
<tr>
<td>II. 3.1% per year</td>
<td></td>
<td>II. 6 bleeds in 79 pts with mean follow-up of 16months</td>
<td>II. Haemorrhage rate in those presenting with haemorrhage or focal neurological deficit</td>
</tr>
<tr>
<td>III. 0.4% per year</td>
<td></td>
<td>III. 1 bleed in 31 pts with unclear follow-up period</td>
<td>III. Rate in the group presenting with presentations other than haemorrhage or focal neurological deficit</td>
</tr>
</tbody>
</table>

A systematic review of the literature on intracranial cavernous malformations 59
The nature, frequency and natural history of intracranial cavernous malformations in adults

Table 8 continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Haemorrhage</th>
<th>N</th>
<th>Details of rates</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim 1997</td>
<td>I. 2.3% per year (1.4% per lesion per year)</td>
<td>62</td>
<td>I. No clear detail of number of bleeds or of group size but there was 2509.6 patient years of follow-up</td>
<td>I. Retrospective rates assuming a constant annual rate since birth</td>
</tr>
<tr>
<td></td>
<td>II. 3.8% per year (2.6% per lesion per year)</td>
<td></td>
<td>II. 2 bleeds in 28pts with mean 22.4 months follow-up</td>
<td>II. Rebleed rate</td>
</tr>
<tr>
<td>Abdulrauf 1999</td>
<td>9.5% haemorrhage rate</td>
<td>55</td>
<td>4 bleeds in 42pts. No data on follow-up period.</td>
<td></td>
</tr>
<tr>
<td>Moriarty 1999</td>
<td>3.1% per year</td>
<td>68</td>
<td>11 haemorrhages in 68pts with 352.9 patient-years of follow-up.</td>
<td>Based on prospective follow-up</td>
</tr>
<tr>
<td>Barker 2001</td>
<td>I. 14% in the 1st year after first bleed</td>
<td>141</td>
<td>82 re-bleeds in 141pts. Some were multiple bleeds in the same patient. No clear details of follow-up</td>
<td>I. Retrospective study. All patients had presented with bleeding so these are really cumulative re-haemorrhage rates over time</td>
</tr>
<tr>
<td></td>
<td>II. 34% 2 years after 1st bleed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>III. 56% 5 years after 1st bleed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV. 72% 10 years after first bleed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantu 2005</td>
<td>1.71% per patient per year</td>
<td>133</td>
<td>78 bleeds in 133pts with 4561 patient-years of follow-up</td>
<td>Retrospective haemorrhage rate assuming that cavernomas are congenital</td>
</tr>
</tbody>
</table>
The nature, frequency and natural history of intracranial cavernous malformations in adults

In the context of cavernoma outcomes during untreated follow-up, in particular haemorrhage excites a lot of interest because of its potentially devastating consequences. What patients really need to know is what the first ever haemorrhage rate is and, also, what the re-haemorrhage rates of untreated cavernomas are. I have listed the various ‘haemorrhage rates’ published in the largest and best studies of prognosis (table 8). There is an enormous variation between studies. Much of the difficulty is with the varying selection of patients which leads to very different types of cohorts and consequently very different outcome rates.

Compounding this problem is the variety of methods used to calculate haemorrhage rates (table 8). Is it retrospective or prospective data collection, per lesion or per patient rates, first ever haemorrhage, re-haemorrhage or a combination of these, and, last but not least, is it clear what denominator is used to calculate haemorrhage rate?

For many studies there is an assumption that cavernomas are congenital and therefore the denominator used is the period of exposure to risk of outcomes being from birth to presentation. However it is now clear that cavernomas are acquired at an unpredictable time throughout life which makes estimation of the period at risk of outcomes much more complex. A much more realistic approach, although imperfect, is to take the period at risk of outcomes from the date of presentation to the end of prospective follow-up. Most rates are formed from a combination of these features but this makes comparison between studies very difficult and no study on its own is powered enough or representative enough of the general population to draw clinically useful conclusions.
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Another major issue that is mentioned in section 3.4 on presentation, it is the lack of uniformity between studies on what constituted a definition of an objective outcome/clinical event, such as haemorrhage, focal neurological deficit and epilepsy. This clearly impedes meta-analysis or even informal comparison between studies and is likely to be responsible in part for the variation in prognosis in the literature to date. The importance of improving this flaw in studies thus far has been addressed in terms of haemorrhage by the Angioma Alliance Scientific Advisory Board [Al-Shahi, 2008] but also in epilepsy in the article by Josephson [Josephson, 2011].

A final idea arising from my review of the literature is whether any studies identify significant prognostic factors. Currently cavernoma location (i.e. brainstem etc.), previous haemorrhage and being female have all been raised as potential prognostic factors of interest but no study is powered enough or appropriately designed to answer these questions definitively. As illustrated in a paper by Counsell et al [Counsell, 2001], for a study of prognosis to be large enough to identify variables that predict a certain outcome there has to be a ratio of at least 10 outcomes to one potential prognostic variable. Therefore to test a prognostic model with two variables one must have at least 20 outcomes of interest. In disease such as intracranial cavernomas the condition is sufficiently rare and the occurrence of outcomes such as haemorrhage sufficiently infrequent to result in many studies being inadequately powered to determine a reliable prognostic model. The solution is to have a large cohort of patients or a smaller cohort that one follows for a very long time. Either
The nature, frequency and natural history of intracranial cavernous malformations in adults

option is not easily attainable and likely explains why we don’t have well developed
diagnostic models to date.

3.5.3 Conclusion

Operating in isolation without consensus definitions among the research community
interested in cavernomas just leads to ambiguous outcomes from small studies that
are difficult to translate into clinically useful information. For the future, widespread
agreement on a clinically relevant outcome definition would have beneficial
implications not just for one study but for all the patients and researchers interested
in this area.

3.6 Treatment in the literature

There are three ways to treat intracranial cavernous malformations – surgical
excision, radiosurgery (LINAC or Gamma knife), or to do nothing but medically
manage symptoms. There are technical considerations to take into account when
pondering the merits of surgical excision versus radiosurgery but I want to take one
step back and consider the debate about whether to intervene at all. We would do
well at this point to bear in mind the historic Hippocratic Oath - First do no harm!

What is published in the literature to date are multiple case series reporting benefit to
highly selected groups of patients based almost exclusively in single surgical centres.
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There are no randomized controlled trials for treatment of cavernous malformations published in the literature [Chapter 3, Section 3.2]. However I note that in January 2013 a center in New Mexico has registered the first trial of medical treatment aiming to reduce risk of haemorrhage in the familial form of cavernomas (http://clinicaltrials.gov). While we await this trial we must make do with the available published data which has belying it an assumption that we know what the untreated prognosis of cavernomas is and therefore know who to select to benefit from what treatments we have. I would seriously dispute this for the reasons outlined in my thesis so far.

There is another fundamental problem with drawing any conclusions from the published data. There is no doubt that literature is heavily influenced by publication bias [Easterbrook, 1991]. The temptation by researchers to seek to publish good results and also by editors and reviewers to publish papers that have something new to offer is very real indeed. With certainty we can say that both surgical excision and stereotactic radiosurgery are not benign interventions. They carry a real morbidity and also mortality. If patients are to make an informed, rational choice about proceeding to active intervention versus none they need to balance up the known untreated prognosis of cavernomas and the known risks and benefits of surgery in some form. I would argue that we have insufficient evidence of all three of these factors.
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There is no doubt that there will be a subgroup of patients who will ultimately benefit from a form of treatment. The challenge lies with us to hold our nerve, establish good evidence of untreated prognosis and then, and only then, pursue who is best to select for surgical treatment. A randomized controlled trial is the only robust way to do this but I am unsure whether this will ever come about in reality, in part because many of these patients are under the care of neurosurgeons!
Chapter 4:

The incidence of intracranial cavernous malformations in SIVMS
The nature, frequency and natural history of intracranial cavernous malformations in adults

4.1 Introduction

The Scottish Intracranial Vascular Malformation study (SIVMS) was set up in 1998. It is a prospective, population-based disease register recruiting incident cases of intracranial vascular malformations in Scotland [Al-Shahi, 2003]. Although all major types of IVMs were recruited and followed in SIVMS, this thesis refers only to those intracranial CMs recruited between January 1st 1999 and December 31st 2003. As my systematic review of the literature revealed, there are major methodological flaws in the designs of studies published in the literature to date. SIVMS was designed to minimise these issues and the impact they would have on results. Therefore it is important for me to outline the methods of SIVMS relevant to each topic under discussion in each chapter, justifying why it is the ideal vehicle for data collection for this thesis.

4.2 Patient recruitment (SIVMS)

At the time of this project in the UK, multicentre research was defined as taking place over five or more local research ethics committees (LREC) geographical boundaries, each LREC usually corresponding to a part or the whole of a health board. Therefore the creators of SIVMS had to submit an application for ethical approval to a multicentre research ethics committee (MREC) for adjudication on the ethical and scientific merit of the project. Once approved (MREC/98/0/48), it had then to be distributed to every LREC in Scotland to judge the suitability of the local site, researcher(s) and facilities before the research could start in their area.
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The methods used in the study are founded on the widely accepted good practice for a study of incidence and prognosis as outlined in Sackett’s Clinical Epidemiology. Scotland's population is a manageable size for such a study and should provide adequate numbers for meaningful data analysis with an estimated incidence for intracranial vascular malformations (IVM's) of 1 to 2.5 per 100,000 of the population per year [Al-Shahi, 2003].

There are four neuroscience centres in Scotland based in Glasgow, Edinburgh, Dundee and Aberdeen. The clinicians, radiologists and pathologists working in clinical neurosciences and stroke medicine provided the main source of cases for SIVMS, based not only at these four neuroscience centres but also at other hospitals throughout the country. Collaborators received monthly newsletters and regular reminders about the study by e-mail and postcard. The SIVMS steering committee updated quarterly lists of potential new collaborators.

In January 2000, my predecessor, Dr Rustam Al-Shahi, contacted all 3,700 GPs in Scotland and asked directly whether any of their patients harboured an IVM. Replies were cross-checked with the patients already known to this study. As the yield of new patients was so low this process was not repeated during my tenure of the Research Fellowship.
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Few patients receive healthcare outside the National Health Service (NHS) in Scotland and there is negligible overseas or cross-border travel to England for healthcare. In Scotland every episode of hospital care is coded by the information and statistics division (ISD) of the NHS with details of a patient’s main diagnosis, comorbidity (up to 5 subsidiary diagnoses), and any operations/procedures performed. These are coded using the 10th revision of the International Classification of Diseases (ICD-10) and are known as the Scottish morbidity records (SMR01). Since 1980 these are linked by the ISD with the death records from the General Register Office (GRO). SIVMS, every six months, received from the ISD records of every person aged 16 or more years either dying or discharged from hospital with an intracranial vascular malformation(s) (IVM). The ISD data supplied in July 2004 completed the dataset from January 1999 to December 2003 (inclusive) and are used in this thesis.

My main duties as the Research Fellow were to collect and review all the clinical material of cases notified to SIVMS by the multiple overlapping sources of case ascertainment. Then I would arbitrate with the relevant expertise where there was doubt about whether the case met the criteria for inclusion in SIVMS.

Only adults (≥ 16 years) have been included in SIVMS because of the different consent procedures for children and also the likely differing aetiology of cavernomas presenting in childhood and their possible differing prognosis.
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4.3 Diagnostic criteria (SIVMS)

Inclusion in SIVMS necessitated meeting the following criteria at the time of diagnosis (table 9):

Table 8 SIVMS inclusion criteria

<table>
<thead>
<tr>
<th>SIVMS inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any of the principal subtypes of IVM(^1)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>• Date of first-in-a-lifetime diagnosis (by imaging or histology) (\geq) 1(^{st}) January 1999</td>
</tr>
<tr>
<td>• Age (\geq) 16 years at the time of this diagnosis</td>
</tr>
<tr>
<td>• Permanently resident in Scotland at the time of this diagnosis</td>
</tr>
</tbody>
</table>

\(^1\) SIVMS recruits adults with any type of IVM, but this thesis only deals with cavernous malformations.

The last two criteria were usually met at notification. Whether it was a new diagnosis or not was concluded by the Research Fellow after review of the clinical casenotes. Definite diagnosis was made based on radiology or pathology and will be discussed in more detail here.

Calcification, or an area of high attenuation without any surrounding oedema on CT imaging can raise the possibility of a cavernous malformation but this is not enough
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to regard it as a definite diagnosis. Definite features on MR imaging are what is
required to make it a ‘definite’ radiological case included in SIVMS. The particular
features on MR were described by Zabramski et al in 1994 and are listed in section
1.3.3, table 1 Chapter 1 [Zabramski, 1994].

It is not always the case that investigations, whether radiological or pathological,
establish a diagnosis of cavernous malformation beyond all doubt. Brain cavernomas
may be uncertain on imaging because radiological investigation is limited i.e.
inadequate MR sequences have been performed, incomplete imaging follow-up over
time etc. This can happen for a variety of reasons. It may have been clinically
inappropriate to pursue the diagnosis any further, the patient may have declined it, or
more appropriate imaging was not available although this is less likely with the more
widespread availability of MR imaging today. If the patient presents with a large
intracranial haemorrhage this can often obscure the underlying lesion and, usually, it
is with time and repeated follow-up imaging that it becomes evident.

Inevitably also, certainty of radiological diagnosis is affected by variation between
observers reflecting experience and subspecialty interests. For these reasons, the final
decision about radiological certainty of diagnosis was taken collectively after review
of all diagnostic imaging. Certainty was arbitrated at consensus meetings between
the SIVMS Research Fellow and the two consultant neuroradiologists (Dr Robin J
Sellar, Western General Hospital, Edinburgh and Dr Jo J Bhattacharya, Southern
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General Hospital, Glasgow). If any SIVMS participant was found to have received an incorrect diagnosis of a brain cavernoma after review of all imaging they were then excluded. The consensus decision subcategorized ‘included’ cases into ‘definite’, ‘probable’ and ‘possible’ to facilitate prospective clinical follow-up in the knowledge that some of these cases, with subsequent imaging, might become ‘definite’ cases in the future.

On the other hand certainty of pathological diagnosis was determined from pathologists’ reports of autopsies and specimens from surgical excision, and was not subject to independent review.

For the purposes of data in this thesis however I included only cavernomas with a ‘definite’ radiological or pathological diagnosis attached on August 31st 2004.

4.4 Procedural protocol on receipt of notification of a new case (SIVMS):

Following notification of a newly diagnosed patient SIVMS contacted the patient’s GP and consultant by post. An interval of four weeks from notification was allowed to elapse for a discharge summary and/or brain imaging report to reach the clinician before contact was made. A structured letter sought confirmation of the accuracy of the information supplied by the notifier, permission to access the patient’s case notes, and questions about whether the patient was suitable for SIVMS to approach by post with a consent pack [Appendix 2 & 3].
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Non-responders were contacted by a three-week reminder letter, and again contacted by letter or telephone if necessary [Appendix 4].

If access to case notes was denied on the grounds of cost by a GP, SIVMS negotiated reimbursement and/or agreed to go to the practice to copy the notes. If access to case notes was conditional upon patient consent and the patient had not been deemed to be aware of their diagnosis, SIVMS attempted to gain access at that time to the notes by reassurance that explicit patient consent was not required for this by MREC in Scotland [Appendix 5].

Disagreements between GP and consultant about whether SIVMS should approach a patient with the postal content pack was of most concern because SIVMS strove to obtain consent and questionnaire data from every living patient. SIVMS had little choice but to refrain from approaching the patient when a clinician’s opinion was that they had been reassured about their prognosis and would be worried by an approach from a research study, or that the patient was too anxious or cognitively impaired for postal contact. However, annual GP follow-up was used as an opportunity to review the appropriateness of these decisions. For a patient to be approached with a consent pack they must have been alive, aware of their diagnosis and deemed appropriate for postal contact. Ethics committees regarded direct first communication from the research study to a patient to be unethical (so-called 'cold calling,’). For this reason SIVMS sent a patient consent pack to the patient's GP, asking the GP to sign a preformatted letter introducing SIVMS and then to forward this letter with the consent pack in a prepaid envelope addressed to the patient.
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[Appendix 6]. The consent pack contained a letter from SIVMS to the patient, a consent form, and information leaflet about SIVMS, and a questionnaire requesting simple demographic details [Appendix 7]. On the consent form, patients were asked whether they permitted access to their medical records and whether they were willing to complete annual questionnaires. If necessary, up to two reminders were sent to the GP at three-week intervals. If there was still no response from the patient after a further six weeks, attempt to gain their consent and completion of the questionnaire was abandoned until the annual follow-up procedure started.

At least four weeks after diagnosis, SIVMS enquired about the extent of brain imaging at the hospital where the diagnosis was made (and the referring hospital, if appropriate). The relevant CT, MRI and IADSA (Intraarterial digital subtraction angiography) studies were requested by telephone, and if they were not received within three weeks, non-responders were contacted by telephone again. Once received, hard copies of each completed imaging study were made and transported to the image library filing cabinet at the Institute of Neurological Sciences in Glasgow to await review by the study neuroradiologists at their consensus meetings with the Research Fellow.

In conclusion, SIVMS, as a population-based study with multiple overlapping sources of case ascertainment and robust criteria for diagnosis and inclusion, was the
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4.5.1 Introduction

Incidence of cavernomas in SIVMS has been estimated for the first two years (1999-2000) [Al-Shahi, 2003]. However, this thesis focuses on cavernomas alone and the following results are based on 5 years of incidence data, from January 1999 to December 2003. The aim is to establish a more robust estimate of incidence with tighter confidence intervals. Only cases that have a definite diagnosis on imaging or pathology on December 31st 2003 are included for the purpose of incidence rate estimation for this thesis.

The most recent and time-relevant decennial census available for Scotland was conducted on 29th April, 2001. At that time, the total population was 5,062,011 of whom 52% were female. 4,089,946 (80.8%) were aged≥ 16 years, and 87% were born in Scotland. The size and age structure of the Scottish population for other years of the study were derived from annual between-census estimates. The General Register Office (GRO) produces these estimates using registration of births and deaths as well as data on immigration and emigration (www.gro-scotland.gov.uk).
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Statistical analysis was done using SPSS software version 11.0 or 16.0. Confidence intervals were calculated using Altman’s Statistics with confidence (2nd edition).

4.5.2 Results

Between January 1st 1999 and December 31st 2003 there were 220 notifications to the study of potential incident brain cavernomas in Scotland. A breakdown of the notification sources is demonstrated in figures 5 & 6.

Figure 5 Total number of cavernoma notifications from 1999 to 2003 and their sources
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Figure 6 Subdivision of hospital consultant notifications by speciality

The nation-wide collaborative network contributed by far and away the most (97%). ISD did not contribute any cases that the collaborative network had omitted. GPs were surveyed with a specific single mailshot in 1999 but this yielded one case that no one else had notified to SIVMS. This exercise was not repeated after 1999 as the yield was not of a sufficient size to justify the workload. Also, at that point the study was established and well-advertised and it was felt that a dedicated annual mailshot was not required.

Of the 220 notifications to SIVMS, 205 related to cases that were subsequently included in SIVMS (Fig. 7). Inclusion relied on diagnostic criteria being met after
The nature, frequency and natural history of intracranial cavernous malformations in adults case notes, diagnostic brain imaging and pathology reports were scrutinized. Fifteen notifications were excluded for various reasons which are illustrated in Figure 7. Of the 205 included notifications, 177 referred to definite and 28 to uncertain cases. Only definite cavernomas were included for the purposes of incidence estimation and 177 notifications translated into 137 definite cases since some cases were notified by more than one source.

**Figure 7 Cavernoma notifications and the translation into included and excluded**

Since some cases were notified by more than one source, 177 notifications translated into 137 definite cases.
In our study population there were 137 incident, or newly diagnosed definite cases of brain cavernomas in the Scottish population over the period 1999 – 2003. This equates to an overall crude incidence of 0.67 (95% CIs, 0.56 to 0.79) per 100,000 adults per year. The adult population mid-year estimate for Scotland was used as the denominator (http://www.gro-scotland.gov.uk/). The crude incidence for each year was also calculated and is illustrated in figure 8.

**Figure 8 Crude incidence for each year of the study based on the mid-year population estimate for that year with 95% CIs**

The incidence rates appear to increase year on year for the first three years of the study, although the confidence intervals do overlap. If this is a true finding it is likely
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to relate to bedding in time for the study. In 2002 there was a dip but this may have
been due to factors such as a change in Research Fellow and the inevitable lag in
study publicity during the transition period from one Fellow to another. Rates for
2003 again met the peak rates from 2001. The certainty of these patterns is shaky
however as all confidence intervals overlap and the findings may be just chance.

Incidence of symptomatic brain cavernomas was 0.36 (95% CIs, 0.28 to 0.45) per
100,000 adults per year. Incidence of asymptomatic brain cavernomas was 0.24
(95% CIs, 0.24 to 0.4).
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There appears to be a trend towards peak incidence between the ages of 25 and 55 years although with the overall small numbers (137 cases) confidence intervals again overlap (Figure 9).

**Figure 9 Age specific incidence for brain CMs in SIVMS with 95% CIs**
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There was no evident significant difference between males and females in different age bands (Figure 10).

**Figure 10 Age and sex specific incidence for brain CMs in SIVMS with either upper or lower limit of each 95% CI shown for clarity**

The incidence for SIVMS, was age standardized against two reference populations. Firstly, the UK population in the 2001 census (http://www.statistics.gov.uk/census2001) and, secondly the USA population in the 2000 census (http://www.census.gov). The incidence rates did not vary significantly between populations suggesting that the age demographics of Scotland are similar to
The nature, frequency and natural history of intracranial cavernous malformations in adults both reference populations and also that our study crude incidence can be translated onto other populations.

The crude incidence was not standardized for sex as there does not appear to be a significant difference between the sexes in our population or in those reported in the wider literature (Fig 10).

4.6 Discussion

As illustrated in my systematic review of the literature methodologically robust studies of the incidence of sporadic cavernomas is significantly lacking. The weaknesses of the studies which are in existence are not from lack of enthusiasm by the researchers but possibly reflect the particular difficulties of doing epidemiological research constrained by availability and cost of resources and also by the ethical issues involved in screening populations for asymptomatic diseases, in particular, diseases where the best course of action, once a diagnosis is established, is not clear.

SIVMS is significant as the first prospective, population-based study to estimate crude incidence based on five years of recruitment; 0.67(95% CIs, 0.56 to 0.79) per 100,000 adults per year. This result is not dissimilar to incidence in the only other truly population based, but retrospective study reported in the literature, 0.5(95%CIs, 1 to 1.0) per 100,000 per year based on a period when MR imaging was available [Brown, 1996]. The incidence calculated by Brown’s study including the period prior
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to MRI availability, resulted in an incidence of 0.17 (95% CIs, 0.34 to 1.0). This
highlights the increasingly significant role that MR plays in the diagnosis of these
lesions. Interestingly in the 10 year period between Brown’s study and SIVMS,
despite the availability and more widespread use of MR, the rates of incidence in
SIVMS did not appear to be that much greater.

The comparison of the incidence of symptomatic intracranial cavernomas in SIVMS,
0.36 (95% CIs, 0.28 to 0.45) per 100,000 adults per year, is probably best done with
the estimated symptomatic incidence from a single surgical centre - 0.32 per 100,000
adults per year [Mathieson, 2003].

In SIVMS the cohort split between symptomatic and asymptomatic was 53%:47%.
In Brown’s population based study it was 40%:60%, not significantly different.
However in Mathieson’s Swedish study, although they claimed it to be population
based, the split was 80%:20% which is more likely to reflect the fact that it was a
single series from a neurosurgical centre. I suspect the truth lies somewhere closer to
our split and Brown’s split although the numbers are so small that only time will tell.
Variation in the use and availability of MR will continue to plague studies of this
nature but eventually with time and larger studies the truth will out.

As discussed previously, the holy grail of studies of incidence is complete case
ascertainment. Although SIVMS is still susceptible to the biases imposed by the
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variable practice between clinicians of investigation of symptoms with imaging and also the potential elusivity of asymptomatic cavernomas, I believe that our comprehensive method of overlapping sources of case ascertainment brings us as close as is currently possible to a true estimate of crude incidence.

To date, the published literature has not raised the possibility of a difference in incidence between the sexes and our results continue to bear this out. Initially, when I came to the project I presumed that the incidence of cavernomas would be significantly greater in young adults due to the pursuit, in clinical practice, of vascular malformations in young stroke victims. Our study suggested a possible tendency for this to be the case but confidence intervals overlap and our results certainly don’t hold this to be definitively true.

Another weakness of SIVMS is the inevitable omission of cases deemed too ill/old for further investigation when presenting with haemorrhage and also those with symptoms too mild for investigation. This, however, is inevitable but the likelihood of these numbers being very small is a source of consolation.

Detection rate versus incidence has been raised in the published literature [Al-Shahi, 2003]. It is true that what we term incident cases are those coming to light for the first time after 1999, whether symptomatic or incidental findings. Although not congenital lesions, cavernomas can exist silently for some time and, therefore, are
more correctly termed prevalent cases. What we call incidence is in fact detection frequency. This is true for many diseases however. Often they exist silently before coming to clinical attention and I believe it is confusing, therefore, to use the semantically correct term ‘detection frequency’ instead of the more widely used and applicable term ‘incidence’.
Chapter 5:

The presentation of intracranial cavernous malformations in SIVMS
5.1 Introduction

The population-based design of SIVMS was ideal to evaluate the relative contribution each subtype of cavernoma presentation makes to the overall disease burden in the Scottish population. As the first multicentre, population-based study SIVMS was breaking new ground.

5.2 Presentation coding in SIVMS

Presentation, or inception into SIVMS, was recorded as the date of the symptom onset that directly lead to a medical evaluation that in turn prompted investigation and a subsequent cavernoma diagnosis. This was the date from which prospective follow-up began. The SIVMS Research Fellow reviewed all available casenotes and then recorded this date in the Microsoft Access database.

At the point where the Research Fellow reviewed the case notes he/she also recorded all the new onset symptoms potentially referable to the cavernoma as clinical events in the database. One such event would correspond to the presentation date in the database and this was how the presentation type was coded for each case in SIVMS. Each clinical event was also coded as ‘definitely’ or ‘possibly’ caused by the cavernoma. At this point also a baseline Rankin score was allocated by the Research Fellow derived from information in the case notes only [Bamford, 1990].
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The study design had pre-specified ‘types of clinical events’ felt to be relevant to cavernomas. Events such as ‘haemorrhage’ that were easily referable to a cavernoma were included but also events such as ‘headache’ where the causal relationship is far less clear. As two different Research Fellows were coding the data collected over five years clear definitions of each type of clinical event were in place prior to patient recruitment.

The clinical events recorded in SIVMS, of which one event would correspond to presentation mode for each patient, were as follows (Table 10):

**Table 9 Presentation/clinical event subtypes in SIVMS**

<table>
<thead>
<tr>
<th>Types of presentation/clinical events recorded in SIVMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental</td>
</tr>
<tr>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Infarction</td>
</tr>
<tr>
<td>Focal neurological deficit persistent</td>
</tr>
<tr>
<td>Focal neurological deficit progressive</td>
</tr>
<tr>
<td>Focal neurological deficit transient</td>
</tr>
<tr>
<td>Epilepsy</td>
</tr>
<tr>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
The nature, frequency and natural history of intracranial cavernous malformations in adults

As the SIVMS Research Fellow for two and a half years, whenever doubt existed in my mind as to how an event/presentation should be coded, the pertinent information was also reviewed by my supervisor, Professor Warlow, and agreed. For the data presented in this thesis the definitions used for coding were as follows;

5.2.1 Incidental

This was coding in the database used for presentations only. There are a few situations when an individual had brain imaging for a completely separate reason and an incidental cavernoma was noted, for example when an individual was acting as a control in a brain imaging study for a purpose unrelated to SIVMS or they had a significant head injury requiring imaging. It may also have been that they had some focal neurology such as unilateral sensorineural hearing loss that was definitely unrelated to the cavernoma.

5.2.2 Intracranial haemorrhage

Clinical features of intracranial haemorrhage with radiological, pathological or surgical evidence, or rarely, only cerebrospinal fluid (CSF) evidence of recent haemorrhage. Radiological proof of acute haemorrhage was fresh blood of high density on CT and/or high signal methaemoglobin on T1-weighted MRI. Very occasionally there was no supplementary evidence supporting a very strong clinical suspicion of haemorrhage and these were coded as ‘clinically probable’ haemorrhages.

The presentation of intracranial cavernous malformations in SIVMS
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5.2.3 Infarction

Classified according to the Oxfordshire Community Stroke Project (OCSP) classification as involving the total/partial anterior circulation, lacunar or posterior circulation.

5.2.4 Focal neurological deficit (FND)

These were defined as clinical impairments referable to the anatomic location of the cavernoma, that were neither definitely post-ictal nor found to be due to haemorrhage or infarction after timely radiological investigation. What constituted timely radiological investigation was more of a pragmatic decision rather than a precise time cut off. It is widely accepted that acute blood transforms from hyperdense to isodense anywhere between 1 to 6 weeks on CT and the signal changes of blood on MR are even more difficult to age in a clinically meaningful way [Bradley, 1993]. Therefore in our study we took ‘timely’ to mean onset of symptoms within 1 week of the scan date (CT in all cases). But if the temporal relationship between symptoms and scan was 8 days and the clinical picture and CT images supported the diagnosis of haemorrhage then it was coded accordingly in the SIVMS database after our consensus meetings with the two neuroradiologists.

FND – persistent (>24 hours)

FND – progressive (>24 hours with further deterioration)

FND – transient (lasting <24 hours)
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Difficulty arose in distinguishing clinically probable haemorrhages from focal neurological deficits not investigated at the right time or with the appropriate type of imaging.

5.2.5 Epilepsy

Any occurrence of an epileptic seizure was classified according to the revised International League Against Epilepsy

Subtypes of epilepsy

- Simple partial +/- secondary generalisation
- Complex partial +/- secondary generalisation
- Generalised
- Status epilepticus
- Unknown

This was recorded within the limits of the data available in the patient’s case notes or from a patient’s annual postal epilepsy questionnaire. Information was also recorded at every opportunity in the notes or in questionnaires about epilepsy activity, treatment and timing of seizures.
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5.2.6 Headache

Type of headache was classified according to the International Headache Society (IHS) classification. In SIVMS most headaches were recorded as migraine, tension-type headache or unknown. An estimate of frequency was also recorded where possible from case notes or questionnaires. As this was a very difficult symptom to attribute to cavernomas, its cause was always recorded as ‘unknown’ in the database pending resolution of this issue in the literature.

5.2.7 Cognitive impairment

This was simply recorded from the case notes without quantification of severity. The aetiology of this event was also recorded as ‘unknown’.

5.2.8 Other

It encompassed a variety of symptoms and signs that may have been attributable to a cavernoma but did not fall under any of the other categories.

Each presentation was coded according to these ten categories and a causal relationship between the event and the cavernoma was also assessed. Much of the analysis focuses on symptomatic versus asymptomatic presentation as clinically this division is often of interest. Throughout this thesis incidental presentations are interchangeable with asymptomatic presentations of cavernomas.
5.3 The presentation of cavernomas in SIVMS

Between January 1999 and December 2003 there were 139 prospectively collected definite cavernoma cases included in SIVMS (Two cases who presented in December 1998 were included in this analysis but were not included in the incidence analysis – n = 137). The presentation details of 138 were available for inclusion in this thesis. One patient’s details were missing from our analysis as the notes were not available to me at the time of writing despite considerable efforts to get them. The details of the assembled cohort are as follows:

5.3.1 Descriptive statistics

5.3.1.1 Sex

78 (56%) were female and 61 (44%) male

5.3.1.2 Age at first presentation

Table 10 Age at first presentation

<table>
<thead>
<tr>
<th>Data available</th>
<th>138/139 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>44</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>16</td>
</tr>
<tr>
<td>Median</td>
<td>40.5</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>32 to 53</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>17, 83</td>
</tr>
</tbody>
</table>
The nature, frequency and natural history of intracranial cavernous malformations in adults

5.3.1.3 Mode of presentation

Table 11 Mode of presentation

<table>
<thead>
<tr>
<th>Mode of presentation</th>
<th>n (%)</th>
<th>n (%), 95%CI of all presentations</th>
<th>n (%), 95%CI of symptomatic presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic¹</td>
<td>65 (47%)</td>
<td>65 (47%, 39% to 55%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic²</td>
<td>73 (53%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>-</td>
<td>34 (25%, 18% to 32%)</td>
<td>34 (47%, 36% to 58%)</td>
</tr>
<tr>
<td>FND (all types)</td>
<td>-</td>
<td>21 (15%, 10% to 22%)</td>
<td>21 (29%, 20% to 40%)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>-</td>
<td>18 (13%, 8% to 20%)</td>
<td>18 (25%, 16% to 36%)</td>
</tr>
<tr>
<td>Total</td>
<td>138 (100%)</td>
<td>138 (100%)</td>
<td>73 (100%)</td>
</tr>
</tbody>
</table>

¹ ‘Asymptomatic/Incidental’ presentations constitute the group of cases with a presentation clinical event such as headache, other, infarction, tinnitus/bruit, cognitive impairment, epilepsy, incidental or FND persistent/progressive/transient but all of which were coded in the database as ‘not caused by the CM’ or it was ‘unknown’ whether the CM was responsible or not.

² Symptomatic presentations were those anatomically corresponding to the known cavernoma and therefore could reasonably be assumed to have caused the symptoms.

If there was more than one symptom then the most clinically relevant symptom at that time was used to code the mode of presentation. Also, when the situation arose where a patient presented with a seizure but it was found to be due to acute
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haemorrhage, then their presentation was coded as haemorrhage as this was felt to be the root cause of the symptom.

5.3.1.4 Incidental presentation by the year of first diagnosis

There did not seem to be a definite pattern over time. However, the possible reduction in numbers of ‘incidental’ cases reported to the study in 2001 may again reflect the wind down period of the first research fellow (table 13).

Table 12 Incidental presentation by year of first diagnosis

<table>
<thead>
<tr>
<th>Incidental</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Yes</td>
<td>13 59%</td>
<td>15 58%</td>
<td>10 30%</td>
<td>10 43%</td>
<td>17 50%</td>
<td>65 47%</td>
</tr>
<tr>
<td>No</td>
<td>9 41%</td>
<td>11 42%</td>
<td>23 70%</td>
<td>13 57%</td>
<td>17 50%</td>
<td>73 53%</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The presentation of intracranial cavernous malformations in SIVMS
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5.3.2 Mode of presentation and its relationship to other factors

5.3.2.1 Median age at presentation according to mode of presentation

It appears that asymptomatic cases may present slightly later than symptomatic cases although interquartile ranges overlap to a certain extent (see figure 11).

Figure 11 Median age at presentation (& interquartile range) by mode of presentation
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This led me to explore whether a statistical difference existed between the mean age of presentation in the asymptomatic group versus the symptomatic group. An independent samples t-test was conducted to compare them. There was a significant difference in mean age at presentation between both groups (table 14).

Table 13 Mean age in symptomatic versus asymptomatic group

<table>
<thead>
<tr>
<th>Mode of presentation</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>37.5 to 59</td>
<td>27.5 to 48.5</td>
</tr>
</tbody>
</table>

\( t \) statistic \((136) = 4.08, p < 0.05\) (two-tailed)

This may reflect a greater amount of imaging being performed in older patients for unrelated reasons allowing the presence of the cavernoma to come to light or, perhaps, incidental cavernomas are acquired with age and cavernomas that are going to be symptomatic do so at a younger age. However, does that mean that older patients diagnosed with an asymptomatic cavernoma can rest easy that they have a more benign condition than those presenting in the fourth decade of life? This was addressed in the chapter on prognosis that follows.
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5.3.2.2 Mode of presentation by gender

No significant difference was found between genders when asymptomatic and symptomatic presentation groups were compared (Fisher’s exact two tailed test).

Table 14 Mode of presentation by gender

<table>
<thead>
<tr>
<th>Mode of presentation</th>
<th>n of males (60)</th>
<th>n of females (78)</th>
<th>Total n (138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>29 (47%)</td>
<td>36 (53%)</td>
<td>65 (100%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>31 (42%)</td>
<td>42 (58%)</td>
<td>73 (100%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>20</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>FND</td>
<td>6</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>5</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

In absolute terms, however there was more than double the number of both FNDs and haemorrhages at presentation in women. This was an interesting finding considering the suggestion in the published literature that women have a tendency to haemorrhage more than men [Robinson, 1991] & [Moriarty, 1999]. To question whether this is borne out in terms of statistical significance I carried out the following analysis;
The nature, frequency and natural history of intracranial cavernous malformations in adults

**Mode of presentation (haemorrhage or other) and gender**

Chi-squared p-value = 0.24 No statistically significant association between haemorrhagic presentation and gender.

**Table 15 Mode of presentation (haemorrhage or other) and gender**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>13</td>
<td>17%</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>65</td>
<td>83%</td>
<td>55</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

**Mode of presentation (haemorrhage/FND or other) and gender**

Chi-squared p-value = 0.03 Interestingly once haemorrhagic presentations are grouped together with FND presentations it appears that women are statistically more likely to present like this than men. This could be because FNDs cause disability like intracranial haemorrhage (ICH) or, indeed, FNDs might be occult ICHs. This will be discussed further in section 5.4 (Discussion).

**Table 16 Mode of presentation (haemorrhage/FND or other) and gender**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Haemorrhage or FND</td>
<td>28</td>
<td>36%</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>50</td>
<td>64%</td>
<td>49</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
5.3.2.3 Mode of presentation by number and types of IVM present per patient

Since cavernomas are not infrequently multiple and are also well described on occasion to be accompanied by a venous malformation (a dilated draining vein), I felt it appropriate to explore the effect the presence of either multiple cavernomas or a cavernoma plus a venous malformation might have on mode of presentation (table 18).

The impact of a single CM versus multiple CMs +/- VMs had no statistically significant effect on the presentation being either asymptomatic or symptomatic in our cohort (Fisher’s exact two tailed test).

Table 17 Mode of presentation by number and types of IVM present

<table>
<thead>
<tr>
<th>Mode of presentation</th>
<th>Single CM (% of total n)</th>
<th>Multiple CMs (% of total n)</th>
<th>CM + VMs(venous malformations) (% of total n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>49</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>50</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>22</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>FND</td>
<td>17</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>11</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>99 (72%)</td>
<td>19 (14%)</td>
<td>20 (14%)</td>
</tr>
</tbody>
</table>
5.3.2.4 Mode of presentation and the presence or absence of a retrospective event such as haemorrhage, epilepsy or FND.

Although our follow-up in SIVMS was prospective, when surveying the casenotes, if an event such as haemorrhage, FND or epilepsy was recorded in the notes prior to diagnosis of the CM and entry into SIVMS, we in turn recorded it in the SIVMS database. I then sought to investigate whether symptomatic presentations were more likely to have a ‘retrospective’ event recorded (table 19).

Our cohort bears out the hypothesis that the likelihood of symptomatic presentations having a previous recorded event (haemorrhage, FND or seizure) was greater than asymptomatic presentations. The difference was significant p = 0.025 (Fisher’s exact two tailed test). Interestingly none of the haemorrhagic presentations had any recorded previous events.

Table 18 Mode of presentation +/- retrospective event

<table>
<thead>
<tr>
<th>Retrospective event</th>
<th>Mode of presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic (n=65)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>FND</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Seizure(s)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Any type of event</td>
<td>9 (14%)</td>
</tr>
</tbody>
</table>
5.3.3 Death at presentation

Six patients died at presentation. None were due to the cavernous malformation itself. All six were incidental diagnoses made at the time of the terminal event. Five cases were incidental findings on a post mortem when the cause of death varied from bleeding oesophageal varices, ruptured iliac artery aneurysm, road traffic accident, bronchopneumonia to murder. The sixth person died of a spontaneous, unrelated subarachnoid haemorrhage and the cavernoma was diagnosed incidentally on imaging.

5.4 Discussion

The results from SIVMS are the first from a large, truly prospective, population based inception cohort and therefore, I suggest, are the closest to the true natural history of cavernomas. Our consistent, clinically relevant and transparent definitions of modes of presentation, such as haemorrhage, make our results practical for translation into every day clinical practice and also useful for other future studies.

Although haemorrhages and focal neurological deficits are distinct presentations/outcomes in cavernomas, there is a certain degree of overlap between the two that is important to discuss. This overlap arises from the grey area of when someone has symptoms referable to the cavernoma that could fit the clinical scenario for either classification and the only distinguishing feature is what is or is not present on timely, appropriate imaging. As SIVMS was an observational study, there was no
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interference in how patients were investigated or managed. The consequences of this were that pursuit of timely imaging in patients with pertinent symptoms varied depending firstly on when the patient reported the symptoms, who they were reported to and what the access to imaging was in that particular region. Therefore if there was delay in imaging for whatever reason, it became difficult to code the clinical event in the knowledge that either coding category - ‘clinically probable haemorrhage’ or ‘true focal neurological deficit without imaging support’ were possible truths. The inevitable overlap between these two groups is difficult to overcome and is why I have analyzed the pertinent data on presentation, and also prognosis in the chapter that follows, in two ways. I felt analyzing results with haemorrhages in a group alone was too simplistic and missed out on part of the story of cavernomas. Putting haemorrhages and focal neurological deficits together in an analysis appears to be justified by the statistically significant finding that women are more likely to present with haemorrhage or focal neurological deficit than men.

If I could do it all over again, I think that our clinical event, ‘focal neurological deficit’, could be more clinically relevant if we had refined our coding into ‘non haemorrhagic focal neurological deficit’ and ‘focal neurological deficit not otherwise specified’, the distinguishing feature being timely imaging supporting or refuting the presence of haemorrhage. This clarity would facilitate analysis in SIVMS but also between SIVMS and any other similar studies in the future.
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Not only is SIVMS the only prospective population-based study but it also has the largest number and proportion of sporadic, asymptomatic cavernomas in the literature (n = 65, 47%). It is interesting that asymptomatic cavernomas tended to present slightly later but, as I will show in the subsequent chapter on prognosis, it doesn’t appear that overall this presentation indicates a more benign clinical course.

In symptomatic presentations in SIVMS, the ranking of epilepsy, focal neurological deficit and haemorrhage in decreasing order of frequency is probably as one would expect in a population-based study. The dramatic and sudden effect that haemorrhage can have on an individual’s life can sometimes overshadow the fact that the greater population burden is due to epilepsy. It is important to highlight this, as a diagnosis of epilepsy can have huge implications for a young adults life, not to mention the possible side effects of medical therapy to treat it. Also, epilepsy due to a structural abnormality tends to be more pharmacoresistant. Many earlier studies focused on those presenting with haemorrhage, perhaps now we should address more closely the issues that epilepsy raises for patients with cavernomas.

Fourteen percent (n = 19) of the cohort had multiple cavernomas. It is sobering that the literature suggests many of these are likely to have a familial form of the disease. Currently there is no policy to screen patients of relatives with multiple cavernomas. How this should be addressed in an observational study is an interesting question. One of the key considerations should probably be – what is the risk of significant
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morbidity or death in relatives of those with multiple CMs? This could be the subject of a whole other thesis!

Again fourteen percent (n = 20) of the SIVMS cohort had an accompanying venous malformation. The significance of this is mainly in terms of technical complexity of surgery. It doesn’t appear to have significant impact on the mode of presentation.

In conclusion, this data from SIVMS adds to the quality of evidence in the literature about cavernoma natural history.
Chapter 6:

The prognosis of intracranial cavernous malformations in SIVMS
The nature, frequency and natural history of intracranial cavernous malformations in adults

6.1 Introduction

As I have mentioned previously, it was the study design of SIVMS that made the assembled cohort a valuable resource for analyses such as prognosis. I will first summarise the procedures for follow-up in SIVMS and then will look at the prognosis.

The cohort of patients used in this analysis were those recruited to SIVMS between January 1st 1999 and December 31st 2003. The follow-up data used in the analysis was that available to me on 31st August 2004.

6.2 Annual follow-up procedures in SIVMS

Patients were followed up on an annual basis during their lifetime by SIVMS using several overlapping methods.

Every patient's GP was contacted six weeks before the anniversary of the patient's diagnosis. A single page GP questionnaire sought confirmation of the patient's address and enquired about whether they were still suitable for postal contact, or whether it was now appropriate to send a postal consent pack if it had not been before. The questionnaire also asked about hospital visits/admissions in the preceding year, the occurrence of brain haemorrhage and epilepsy, and asked the GP to assess the patient's current disability on the modified Rankin scale [Bamford, 1990], [Appendix 8]. A reminder letter was sent after three weeks [Appendix 9], and
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GPs were telephoned after a further three weeks if they still had not replied. A copy of the GP casenotes amassed over the last year and also copies of casenotes from any hospital visits were reviewed by the SIVMS Research Fellow and any relevant outcomes were recorded in the database.

Patients were contacted directly, if appropriate, about the occurrence of headaches and seizures or fits [Appendices 10, 11 & 12]. When a patient died a copy of the patient’s death certificate was obtained from the GRO and an autopsy report requested if a post-mortem was performed.
6.3 Assessment of disability in SIVMS; Modified Rankin scale

This well established scale for quantifying the morbidity associated with many medical conditions was recorded at presentation by the Research Fellow from information available in the casenotes. Thereafter it was recorded annually for patients in SIVMS where possible based on the GP or patient annual questionnaire [Appendices 8 & 10].

Table 19 Modified Rankin Scale

<table>
<thead>
<tr>
<th>Symptom level</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>0</td>
</tr>
<tr>
<td>Minor symptoms, which do not interfere with lifestyle</td>
<td>1</td>
</tr>
<tr>
<td>Some restrictions to lifestyle but looks after oneself</td>
<td>2</td>
</tr>
<tr>
<td>Significant restriction to lifestyle, preventing total independence</td>
<td>3</td>
</tr>
<tr>
<td>Severe handicap preventing independent existence, but not requiring constant attention</td>
<td>4</td>
</tr>
<tr>
<td>Severe handicap, totally dependent, requiring attention day and night</td>
<td>5</td>
</tr>
<tr>
<td>Dead</td>
<td>6</td>
</tr>
</tbody>
</table>
6.4 The prognosis of cavernomas in SIVMS

I used Kaplan Meier analysis and survival plots to illustrate the survival and ‘time to event’ data for the patients in SIVMS. SPSS version 16.0 software was used to conduct these analyses.

In the analysis patients were censored at the relevant date of outcome, date of death or date of last follow-up.

6.4.1 Prognosis analysis using primary outcomes

6.4.1.1 All cause mortality

Six patients presented dead and during follow-up eight more patients died. Of those eight, three deaths were due to cavernoma and five due to other causes.
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Figure 12 All cause mortality

![Mortality Graph]

Number at risk 139 109 82 48 27 11

6.4.1.2 Death due to cavernoma alone

One of the three deaths due to cavernoma had been treated with surgical excision. Their death was almost two years after surgery and was due to a seizure (Treatment 6/3/02, death 2/1/04). The seizure disorder also predated their surgery.

The second death was due to choking precipitated by haemorrhage from the cavernoma.

The final death was due to a chest infection as a consequence of a persistent focal neurological deficit caused by the brainstem cavernoma.
6.4.1.3 First or recurrent haemorrhage during follow-up due to cavernoma

Six patients had a haemorrhage after presentation. One of these six patients had two haemorrhages during follow-up.

Five out of the six haemorrhages were in women.

Treated patients were not censored at their treatment date in this graph. Two patients who haemorrhaged were treated but this was after their haemorrhage had occurred.

Figure 13 First or recurrent haemorrhage in all cavernomas
6.4.1.4 FND during follow-up in all cavernomas

Treated patients were not censored at their treatment date in this graph. Five of the nineteen patients who had FNDs were treated. Four of those five were treated before the FND but very close in time to it. One was treated after the FND had occurred.

Figure 14 FND in all cavernomas
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6.4.2 Prognosis analysis using composite outcomes and stratifying features

In this section I use the composite outcome of haemorrhage and focal neurological deficit. The logic of this was discussed in Chapter 5 on presentation and the same logic holds true here for outcomes.

6.4.2.1 The outcomes during follow-up; Haemorrhage and haemorrhage/FND stratified by asymptomatic versus symptomatic presentation

My analysis of presentation showed that asymptomatic cavernomas presented a decade later than symptomatic ones. This led me to pursue whether asymptomatic cavernomas have a more benign clinical course. I therefore investigated any statistical differences that could be demonstrated between the number of haemorrhage or haemorrhage/FND outcomes seen in the asymptomatic versus symptomatic presentation groups (figures 15 & 16).
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Figure 15 Haemorrhage during follow-up in asymptomatic versus symptomatic presentations

Figure 16 Haemorrhage/FND during follow-up in asymptomatic versus symptomatic presentation
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Both figures illustrate the finding that there was no significant, or indeed clinical
difference between the survival curves in the asymptomatic presentation versus the
symptomatic presentation groups despite the statistically significant difference in
mean age at presentation.

6.4.2.2 First or recurrent haemorrhage or FND during follow-up stratified by
haemorrhagic presentation versus other presentation

Treated patients were not censored at their treatment date in this graph.

Three patients who had FNDs were treated. Of those three one surgical excision was
performed after the FND occurred and the other two had surgical excision prior to
the occurrence of their FND although the surgery and FND were very close in time.

Two patients who haemorrhaged were treated by surgical excision but this was after
their haemorrhage had occurred.

Mantel-Cox Log Rank test was used for comparison of survival curves between
those presenting with haemorrhage and those not. There was no statistically
significant difference (p = 0.103) although the number of cases presenting with
haemorrhage were comparatively few.
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Figure 17 Haemorrhage/FND during follow-up stratified by haemorrhagic presentation versus other

<table>
<thead>
<tr>
<th>Years since presentation</th>
<th>Proportion of patients event free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
</tr>
<tr>
<td>3</td>
<td>0.85</td>
</tr>
<tr>
<td>4</td>
<td>0.80</td>
</tr>
<tr>
<td>5</td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>0.70</td>
</tr>
<tr>
<td>7</td>
<td>0.65</td>
</tr>
<tr>
<td>8</td>
<td>0.60</td>
</tr>
<tr>
<td>9</td>
<td>0.55</td>
</tr>
<tr>
<td>10</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**Presentation**
- Other
- Haemorrhage

**Number at risk:**
- Haemorrhage: 17, 10, 6, 1
- Other: 122, 92, 63, 43, 22, 7

6.4.2.3 First or recurrent haemorrhage or FND during follow-up stratified by haemorrhagic/FND presentation versus other presentation

Treated patients were not censored at their treatment date in this graph. Three patients who had FNDs were treated. Of those three one surgical excision was
The nature, frequency and natural history of intracranial cavernous malformations in adults performed after the FND and the remaining two had surgical excision prior to the occurrence of their FND although the surgery and FND were very close in time.

Two patients who haemorrhaged were treated by surgical excision but this was after their haemorrhage had occurred.

**Mantel-Cox Log Rank test** was used for comparison of differences in survival curves between those presenting with haemorrhage or FND and those not. There was a significant difference ($p < 0.05$).

**Figure 18** Haemorrhage/FND during follow-up stratified by haemorrhage/FND presentation versus other

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Years since presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients event free</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>0.55</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Number at risk:**

<table>
<thead>
<tr>
<th>Haemorrhage/FND</th>
<th>52</th>
<th>35</th>
<th>22</th>
<th>13</th>
<th>7</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>87</td>
<td>67</td>
<td>47</td>
<td>30</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>
6.4.2.4 First or recurrent haemorrhage or FND during follow-up stratified by gender

In Chapter 5 it was shown that women were statistically more likely to present with haemorrhage or focal neurological deficits. When this was combined with the information in figure 18 illustrating a significant difference in the survival curves in terms of the composite outcome haemorrhage/FND for those presenting with haemorrhage/FND or not, I wondered whether this difference in survival curves for the composite outcome would also be true if it was examined for gender. Knowledge that five out of six haemorrhages and fourteen out of nineteen FNDs were in women added to my curiosity.

Figure 19 Haemorrhage/FND during follow-up stratified by gender
Mantel-Cox Log Rank test was used for comparison of differences in survival curves between males and females for the composite outcome haemorrhage/FND. There was a significant difference (p < 0.05). Women appeared to have a greater statistical chance of haemorrhage or FNDs than men.

6.4.3 Disability in SIVMS

6.4.3.1 SIVMS Modified Rankin scores at presentation and at 1 year

At presentation 13% of the cohort had a Modified Rankin score of ≥3. For all modes of presentation table 21 illustrates the amount of significant disability in the SIVMS cohort at the end of the first year after presentation as assessed by the modified Rankin scale.

At the end of year one, 16% of the cohort had a Rankin of ≥ 3. Rankin scores were missing for 13 patients all of whom had not reached their first anniversary prior to the study end date.
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Table 20 Modified Rankin score 1 year after presentation

<table>
<thead>
<tr>
<th>Rankin</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>45</td>
<td>32%</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>19%</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>7%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Dead</td>
<td>8</td>
<td>6%</td>
</tr>
<tr>
<td>Missing data</td>
<td>13</td>
<td>9%</td>
</tr>
</tbody>
</table>

Overall the disability burden in the cohort does not appear to have changed in one year into follow-up.

6.5 Discussion

As my systematic review highlighted, calculating simple rates of outcomes for patients with cavernomas can be misleading and unhelpful. A particular, insurmountable difficulty is to do with the unknown date of biologic onset. I propose, therefore, that Kaplan Meier analysis/survival curves of early prospective follow-up, which can also factor in censored patients, is a much more meaningful way of looking at prognosis after presentation in this population. The useful conclusions that we were able to draw for patients with cavernomas from our prospective, population-based data is as follows:
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- All cause mortality – three years after presentation 87% of the cohort were alive

- Death due to cavernoma – the three deaths in SIVMS during follow-up, known to be caused by the cavernoma, were evenly distributed between haemorrhage, epilepsy and focal neurological deficit.

- First or recurrent haemorrhage during follow-up – two years after follow-up 94% of the cohort were haemorrhage free

- Focal neurological deficit (FND) – three years after presentation 80% of the cohort were FND free

- Being female or presentation with the composite event - haemorrhage or FND - had a statistically significant impact on making one more likely to either haemorrhagic or FND outcomes during early follow-up.

- Asymptomatic presentation appeared to have no impact on the likelihood of a haemorrhagic or FND outcome during early follow-up.

- Haemorrhagic presentation alone also appeared to have no statistical impact on the likelihood of a haemorrhagic or FND outcome during early follow-up.

- In our cohort, the proportion of patients with a modified Rankin score of ≥ 3 did not change significantly between presentation (13%) and the end of year 1 (16%).
Our data would seem to suggest that most haemorrhages or focal neurological deficits that occur during follow-up appear to occur in the two to three years after presentation and then events seem to plateau. At three years follow-up however, our numbers are very small and therefore this finding is unsound. As SIVMS continues follow-up this will be an interesting trend to observe.

Being female or presentation with haemorrhage or FND predict poorer outcome in terms of haemorrhage or FND in early follow-up. These factors may well be interrelated. In Chapter 5 we found women were more likely to present with haemorrhage or FNDs than men. That aside, our finding supports the literature to date that there is a hormonal effect putting women at greater risk of haemorrhage than men (section 1.1.3). The mechanism of how this happens is still unproven however.

In Chapter 5 I discussed the logic of amalgamating haemorrhagic outcomes with FNDs. There is clear overlap between the two groups but not complete overlap. Therefore, as I mentioned previously, I think a more clinically relevant outcome would be ‘definite non haemorrhagic FND’ and ‘FND with no timely imaging’. This is what has been proposed by the Angioma Alliance Scientific Advisory Board in 2008 [Al-Shahi, 2008]. This would aid sensitivity analysis within SIVMS and also between similar studies.
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Another final observation from our cohort is that being asymptomatic at presentation is of no benefit in terms of subsequent prognosis of haemorrhage or FND. This is an important observation as to date most patients selected for treatment are those with haemorrhagic presentations or intractable epilepsy. Our results suggest that this is not logical.

SIVMS has provided an invaluable dataset for establishing the early prognosis of patients with intracranial cavernous malformations. Since the conclusion of the dataset used for this thesis, follow-up of our cohort has been continued by others who became involved with SIVMS after my period as Research Fellow. This completed a full 5 years follow-up on each patient and culminated in a recent publication in Lancet Neurology [Al-Shahi et al, 2012]. Longer follow-up confirmed the trends suggested by my data that recurrent events such as haemorrhage and focal neurological deficit appear to cluster in the first couple of years after presentation and then the risk tapers off (the annual risk of recurrence of this composite outcome declined from 19·8% (95% CI 6·1–33·4) in year 1 to 5·0% (0·0–14·8) in year 5) and the risk of a recurrent event is higher for women than men (p=0·01). Also the 5 year risk of a first ever composite outcome such as this was significantly less than the 5 year risk of a recurrent outcome (9·3%, 3·1–15·4 vs 42·4%, 26·8–58·0; p<0·0001). The follow-up continues.
Chapter 7:

The treatment of intracranial cavernous malformations in SIVMS
7.1 Introduction

As discussed in Chapter three, there are no randomised controlled studies of treatment in cavernous malformations. This thesis focuses on the untreated clinical course or natural history of cavernomas. However, some of our 139 patients were treated, but as SIVMS was an observational study we had no impact on who or how this came about. For information, I will detail how these patients were managed but no real conclusions can or will be drawn from these data.

7.2 Treatment of cavernomas in SIVMS

Twenty-four patients in all were treated in our cohort. Twenty-three were treated with complete surgical excision, one with partial surgical excision and none with Gamma-knife radiosurgery.

The decision to go for treatment was made by the clinician and patient together. SIVMS had no input into this.

The average time from presentation to treatment was 303 days.

Of the 24 patients who were treated in SIVMS their breakdown in terms of mode of presentation are as follows (table 22):
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Table 21 Mode of presentation of patients treated in SIVMS

<table>
<thead>
<tr>
<th>Mode of presentation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>9</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>8</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>4</td>
</tr>
<tr>
<td>Focal neurological deficit</td>
<td>3</td>
</tr>
</tbody>
</table>

Four centres offer neurosurgery in Scotland, the breakdown in location where the surgery took place is shown in table 23.

Table 22 Numbers of patients treated subdivided by neurosurgical centre

<table>
<thead>
<tr>
<th>Neurosurgical centre</th>
<th>Number of patients undergoing surgery for their cavernoma (as a % of those treated)</th>
<th>% of the population residing within the catchment area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre A</td>
<td>3 (12%)</td>
<td>8%</td>
</tr>
<tr>
<td>Centre B</td>
<td>13 (54%) (All 4 incidental cases were treated here)</td>
<td>49%</td>
</tr>
<tr>
<td>Centre C</td>
<td>4 (17%)</td>
<td>13%</td>
</tr>
<tr>
<td>Centre D</td>
<td>4 (17%)</td>
<td>30%</td>
</tr>
</tbody>
</table>
7.3 Discussion

SIVMS was an observational study and of our 139 patients included for prospective follow-up, 24 were treated. It is interesting to note that all of these patients were treated with surgical excision and none were treated with radiosurgery (although it is available). Is this because the clinicians responsible were neurosurgeons and more confident in offering a treatment they could deliver themselves? Or the fact that patients would have to cross the border to England for radiosurgery had some impact on the decision process? No matter, the decision to treat was clearly a subjective one. With this in mind and also the small numbers I felt it inappropriate to segregate out treated patient for analysis of prognosis. I felt the data would be misleading and unhelpful and would simply add to the methodologically unsound literature already published.

Reported high re-haemorrhage rates in those presenting with haemorrhage, or epilepsy refractory to medical management, are the two reasons usually cited in the literature as an indication for surgical intervention. In our cohort, of the six patients who haemorrhaged during the early, prospective follow-up period, three of them had presented to the study with an incidental diagnosis, two had presented with haemorrhage and one with a focal neurological deficit. This raises doubt about the selection criteria (predictors of poor prognosis) used for surgical intervention in the literature to date. Also the spread of presentations across the treated patients in SIVMS (table 22) further highlights the lack of uniformity or evidence based decision making that occurs between centres.
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The proportions of patients treated according to neurosurgical centre are broadly in line with the populations of the relevant catchment areas. There is a slight discrepancy between the two middle-sized centres. This could be due to regional differences in practice but is most likely a spurious finding with such small numbers.

In conclusion, evidence regarding the best way to manage patients with cavernomas is scant and the treatments available are not without risk. It is therefore imperative to establish the untreated prognosis of cavernomas so we can proceed to uncovering who is best to treat and with what treatment, short of any randomized controlled trials.
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Chapter 8:

Validity of MR imaging in the diagnosis of intracranial cavernous malformations
8.1 Introduction

The relative contribution of the main imaging modalities (cerebral angiography, CT and MR imaging) to the diagnosis of intracranial cavernous malformations is clear from my introduction in Chapter 1. Anecdotal evidence in the literature supports the theory that MR is superior to CT and angiography combined in the diagnosis of cavernomas. However, as MR imaging is currently used as a screening tool in the familial cavernoma setting I felt it was important to evaluate it as a stand-alone investigation to see whether it could rival histology as a mode of diagnosis. There is no doubt that a non-invasive imaging test providing a definite diagnosis is superior to an excision biopsy or post-mortem specimen but only if it is of adequate sensitivity and specificity. The sensitivity and specificity of MR imaging was therefore important to quantify. Some of the cases included in this study came from SIVMS but that is where the overlap ended. The study design, execution and analysis were separate from SIVMS and will be outlined in the following sections.

8.2 The validity of MR imaging in the diagnosis of intracranial cavernomas; methods

The study design was to compare the sensitivity and specificity of MR in true, pathologically verified cavernous malformations versus commonly encountered mimics.
8.2.1 Cavernoma cases

Pathologically verified cases of intracranial cavernous malformations were sought from the four neuroscience centres in Scotland – Aberdeen, Dundee, Edinburgh and Glasgow. Consent was obtained from the attending consultant to review the pre-operative imaging of each case. Any individual who also had a pre-operative magnetic resonance scan in the last ten years was included in this study. Cases from the SIVMS study were also included. Seventeen cases, with a total of nineteen cavernous malformations, fulfilled all the selection criteria.

8.2.2 Mimic cases

Mimics were more difficult to select. A literature search identified the lesions most likely to be confounders in the radiological diagnosis of cavernomas of the brain [Preul, 1992] & [Olivero, 2000], [Akimoto, 2009], [Becker, 2010], [Buccoliero, 2006], [Bulzico, 2011], [Matsuno, 2005] (table 24).

Table 23 Mimics of cavernomas in the literature

<table>
<thead>
<tr>
<th>Potential mimics from literature search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous haematomas</td>
</tr>
<tr>
<td>Arteriovenous malformations</td>
</tr>
<tr>
<td>Haemorrhagic metastases</td>
</tr>
<tr>
<td>Intraventricular meningiomas</td>
</tr>
<tr>
<td>Choroid plexus papillomas</td>
</tr>
<tr>
<td>Other tumours (astrocytomas, gliomas, etc.)</td>
</tr>
</tbody>
</table>
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The MR scans of cases with any one of these six diagnoses were then selected from imaging libraries accessible to us. Fifty-six cases were identified and given to an independent neuroradiologist (Dr AJ Farrall) to select the best cases for our study. The criteria he sought were MR scans done within the last 10 years whose lesion characteristics on MR imaging would represent the cases a neuroradiologist may find difficult to interpret as a definite cavernous malformation. Eleven cases met with these criteria. The confirmation of the correct diagnosis in each case was made by pathology after surgical excision/biopsy or by follow-up imaging over a significant period of time. The mimics used in this study fell into the following categories (table 25).

Table 24 Mimics used in validity of MR study

<table>
<thead>
<tr>
<th>Diagnosis of mimics used in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1       Solitary metastasis</td>
</tr>
<tr>
<td>1       CSF cyst</td>
</tr>
<tr>
<td>6       Spontaneous haematoma</td>
</tr>
<tr>
<td>2       Arteriovenous malformation with haematoma</td>
</tr>
<tr>
<td>1       Radiation induced vascular abnormality</td>
</tr>
</tbody>
</table>

No MR scan pre-dated 1992. As the cases were ascertained retrospectively, and from different centres, the sequences done varied from case to case. We decided therefore that sequences common only to all scans (T_1 and T_2) should be used for this study. The distribution of sequences used by the reviewing radiologists for both groups are...
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shown in tables 26 and 27 respectively. Originally we assumed that most cases would have included a gradient echo sequence; however only 7 of our 28 scans had this sequence done as part of the original diagnostic workup. This was too few to include in the study and therefore any gradient echo sequences were removed from the study packets for review.
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Table 25 Sequences for cavernomas available for use

<table>
<thead>
<tr>
<th></th>
<th>Table of sequences available for cavernous malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T1 sagittal, T1 axial</td>
</tr>
<tr>
<td>2</td>
<td>T1 axial</td>
</tr>
<tr>
<td>3</td>
<td>T1 sagittal, T1 coronal,</td>
</tr>
<tr>
<td>4</td>
<td>T1 sagittal</td>
</tr>
<tr>
<td>5</td>
<td>T1 sagittal, T1 coronal</td>
</tr>
<tr>
<td>6</td>
<td>T1 axial+contrast, T1 sagittal+ contrast</td>
</tr>
<tr>
<td>7</td>
<td>T1 coronal</td>
</tr>
<tr>
<td>8</td>
<td>T1 axial</td>
</tr>
<tr>
<td>9</td>
<td>T1 coronal</td>
</tr>
<tr>
<td>10</td>
<td>T1 sagittal</td>
</tr>
<tr>
<td>11</td>
<td>T1 sagittal</td>
</tr>
<tr>
<td>12</td>
<td>T1 coronal</td>
</tr>
<tr>
<td>13</td>
<td>T1 axial</td>
</tr>
<tr>
<td>14</td>
<td>T1 coronal</td>
</tr>
<tr>
<td>15</td>
<td>T1 coronal</td>
</tr>
<tr>
<td>16</td>
<td>T1 coronal, T1 axial</td>
</tr>
<tr>
<td>17</td>
<td>T1 coronal</td>
</tr>
</tbody>
</table>

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**Table 26 Sequences for mimics available for use**

<table>
<thead>
<tr>
<th>Table of sequences available for mimics/controls</th>
<th>18</th>
<th>T1 axial, T1 axial + contrast</th>
<th>19</th>
<th>T1 axial, T1 sagittal,</th>
<th>20</th>
<th>T1 axial + contrast</th>
<th>21</th>
<th>T1 axial + contrast</th>
<th>22</th>
<th>T1 axial, T1 sagittal</th>
<th>23</th>
<th>T1 sagittal</th>
<th>24</th>
<th>T1 sagittal</th>
<th>25</th>
<th>T1 axial</th>
<th>26</th>
<th>T1 sagittal</th>
<th>27</th>
<th>T1 sagittal</th>
<th>28</th>
<th>T1 axial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
<td></td>
<td>T2 axial</td>
</tr>
</tbody>
</table>
All cases were unknown to our reviewing radiologists. The observers were five neuroradiologists (table 28) from different centres in England, all of whom had a special interest in vascular abnormalities of the brain. They reviewed independently of each other.

Table 27 The five reviewing neuroradiologists from England and Wales

<table>
<thead>
<tr>
<th>Hospital base</th>
<th>Neuroradiologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkinson Morley’s Hospital, London</td>
<td>A Clifton</td>
</tr>
<tr>
<td>Newcastle General Hospital, Newcastle upon Tyne</td>
<td>A Gholkar</td>
</tr>
<tr>
<td>University Hospital of Wales, Cardiff</td>
<td>S Halpin</td>
</tr>
<tr>
<td>Radcliffe Infirmary, Oxford</td>
<td>A Molyneux</td>
</tr>
<tr>
<td>Newcastle General Hospital, Newcastle upon Tyne</td>
<td>C Soh</td>
</tr>
</tbody>
</table>

8.2.3 Data collection

Hard copies of all 28 scans (30 lesions) were sent to the individual reviewers with a standard data collection form to be completed for each scan [appendix 11]. Each reviewer was asked to answer the following questions:

- What is the *quality of the film*?
• Are there any lesions with imaging characteristics of a cavernous malformation?

• If answer yes, what side and area of the brain is it in?

• Is it a definite cavernous malformation, a maybe or a definitely not cavernous malformation?

• If the maybe option was chosen they were asked what they would like to do next to confirm the diagnosis?

The data were recorded in a Microsoft Access database. All data were double-punched to ensure accuracy of data entry.

### 8.2.4 Data processing and analysis

Calculating the sensitivity and specificity of MR imaging as a diagnostic tool for cavernomas requires a dichotomous dataset. In this study each reviewer was given three options for each lesion – definite yes, maybe and definite no. This was done to reflect, as accurately as possible, the real life diagnostic dilemma faced by clinicians. Therefore when calculating the sensitivity and specificity of MR imaging it was analysed in two ways.

Firstly, what we termed the harsh analysis. When a neuroradiologist prevaricated and chose the maybe option, it was assumed, for that lesion, even if they received the further imaging, which could be requested at this stage, they still got the diagnosis
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wrong and the answers for *maybe* lesions were distributed as though they chose incorrectly between the two groups – definitely yes and definitely no. Now we had a dichotomous dataset to analyse which, in essence, reflected the worst possible scenario for sensitivity and specificity.

In practice this situation is unrealistic. If a radiologist is unsure from the scan in hand what a lesion is, it is common and good practice to do further sequences, or follow-up imaging which clarifies the diagnosis. To reflect this scenario, the more *fair analysis* gave each reviewer the benefit of the doubt and assumed that, if supplied with further sequences or follow-up imaging, they would have correctly diagnosed the lesion for what it was. The *maybe* group were therefore distributed correctly between the definitely yes and the definitely no groups. This in turn gives a best possible case scenario for sensitivity and specificity.

The sensitivity and specificity of each reviewer were calculated. All analyses were performed in Statistical Product for the Social Sciences (SPSS) version 11.0 except confidence intervals which were calculated using Confidence Interval Analysis software [Altman, 2000].

**8.2.5 Ethics**

Every film was carefully anonymized in order to protect patient confidentiality and comply with UK Data Protection legislation. This study was covered under the
The nature, frequency and natural history of intracranial cavernous malformations in adults

approval given for SIVMS by the Multicentre Research Ethics Committee for Scotland (MREC/98/0/48).

8.3 The validity of MR imaging in the diagnosis of intracranial cavernous malformations; Results

The five reviewing consultant neuroradiologists from England each reviewed the identical twenty-eight MR scans (30 lesions). All sets of scans had a mixture of real cavernoma cases and mimics. The reviewers were not privy to the cavernoma: mimic ratio.

A complete set of data was received from all reviewers. There was only little disagreement between reviewers about film quality and therefore the modal rating was taken. The results are shown in table 29.

Table 28 Film quality

<table>
<thead>
<tr>
<th>Film quality</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>18% (5/28)</td>
</tr>
<tr>
<td>Average</td>
<td>68% (19/28)</td>
</tr>
<tr>
<td>Poor</td>
<td>14% (4/28)</td>
</tr>
</tbody>
</table>
The nature, frequency and natural history of intracranial cavernous malformations in adults

The distribution of lesions according to side and brain area are shown in table 30.

There was no overtly dominant location that could account for easier or more difficult recognition of the lesion by the neuroradiologists.

Table 29 Distribution of lesions by side and location

<table>
<thead>
<tr>
<th>Location</th>
<th>Cavernoma (19)</th>
<th>Mimic (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>58% (11)</td>
<td>45% (6)</td>
</tr>
<tr>
<td>Right</td>
<td>42% (8)</td>
<td>55% (5)</td>
</tr>
</tbody>
</table>

**Supratentorial**

- Frontal: 4
- Frontotemporal: 2
- Fronto-parietal: 0
- Parietal: 2
- Temporal: 6
- Temporo-parietal: 2
- Parieto-occipital: 1
- Thalamus: 1
- Occipital: 0

**Infratentorial**

- Cerebellum: 1

If the reviewing neuroradiologists could only give a ‘maybe’ diagnosis for the lesion in question, they were asked to choose what further sequences they would request in a real clinical setting to confirm the diagnosis. Table 31 illustrates the distribution of their choices.
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Table 30 Frequency with which reviewers requested different sequences

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Number of requests</th>
<th>Frequency of request (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>T2</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>FLAIR</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>T1 + contrast</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Gradient echo</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Angio</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Diffusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

As discussed in section 8.2.4 the sensitivity and specificity analysis of this dataset was calculated in two ways – harsh and fair.

The harsh and fair analyses are shown in tables 32 & 33 respectively. The harsh dataset yielded a mean sensitivity of 58% and a specificity of 67% (Table 32). The fair analysis which is akin to a genuine clinical setting yielded a specificity of 100% and a sensitivity of 83% (Table 33).
The nature, frequency and natural history of intracranial cavernous malformations in adults

Table 31 Harsh analysis

<table>
<thead>
<tr>
<th>Radiologist</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>1</td>
<td>74(51-88)</td>
<td>64(35-84)</td>
</tr>
<tr>
<td>2</td>
<td>47(27-68)</td>
<td>100(74-100)</td>
</tr>
<tr>
<td>3</td>
<td>68(46-87)</td>
<td>64(35-84)</td>
</tr>
<tr>
<td>4</td>
<td>53(32-73)</td>
<td>36(15-64)</td>
</tr>
<tr>
<td>5</td>
<td>47(27-68)</td>
<td>73(43-90)</td>
</tr>
<tr>
<td>mean</td>
<td>58</td>
<td>67</td>
</tr>
</tbody>
</table>

Table 32 Fair analysis

<table>
<thead>
<tr>
<th>Radiologist</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>1</td>
<td>84(62-94)</td>
<td>100(74-100)</td>
</tr>
<tr>
<td>2</td>
<td>68(46-84)</td>
<td>100(74-100)</td>
</tr>
<tr>
<td>3</td>
<td>89(69-97)</td>
<td>100(74-100)</td>
</tr>
<tr>
<td>4</td>
<td>100(83-100)</td>
<td>100(74-100)</td>
</tr>
<tr>
<td>5</td>
<td>74(51-88)</td>
<td>100(74-100)</td>
</tr>
<tr>
<td>mean</td>
<td>83</td>
<td>100</td>
</tr>
</tbody>
</table>
8.4 Discussion

This study was a pragmatic effort to quantify sensitivity and specificity of MR imaging as a stand-alone diagnostic tool for cavernomas of the brain. This was the first study of its kind. Many studies have confirmed the superiority of MR imaging over CT imaging or cerebral angiography as a diagnostic tool [Rigamonti, 1988], [Requena, 1991] and there is general acceptance among the radiology community that MR imaging, in particular scans incorporating gradient echo sequences, are the gold standard for diagnosis of brain cavernomas [Brunereau, 2001], [Haque, 2003] and [Lehnhardt, 2005]. This study however shows that, even in the most optimistic clinical setting, although MR is highly specific (mean 100%) sensitivity (mean 83%) still falls short of pathological verification. The disappointing results of our harsh analysis- sensitivity 58% & specificity 67% - probably reflected the inadequacy of T1 & T2 sequences alone.

In this study we focussed solely on the comparison of MR against histopathology as a diagnostic tool. Of course both these tests require human input to interpret and are therefore subject to human error or differences in abilities between reviewers. Attempts are often made in studies of this nature to quantify how well reviewers/observers agree with each other as opposed to agreement arising by chance and conclude from this data something about the robustness of the technique as a diagnostic tool. The kappa statistic is commonly used in the literature for this purpose. However, I did not apply this here because kappa is confined to comparing
The nature, frequency and natural history of intracranial cavernous malformations in adults two reviewers and our study had five (i.e. ten kappa statistics would be required). To do multiple kappas would have been unwieldy and difficult to interpret in a pragmatic way. There are statistical tests such as the Fleiss kappa which can be done with multiple reviewers but after discussion with our statistician, Dr S Lewis, I concluded that this was a pragmatic study with other methodological limitations and to attempt more complex evaluation of interobserver reliability would simply detract from the main messages of the study, firstly, that MR is an excellent diagnostic tool and secondly that gradient echo or SWI imaging should be added to the protocol in assessment of potential intracranial cavernomas.

The ideal circumstances in which this type of study should be executed are very difficult to create – prospective ascertainment of both real, histologically confirmed cases and mimics, standard and reproducible MR study protocols, use of identical scanners and multiple reviewers with little inter-observer variation.

The obvious disadvantage of our retrospective study, is the possibility that the real cases we chose were sent for surgical excision because they presented a diagnostic conundrum. This would account for the poor sensitivity (mean 58%) in the harsh analysis. Added to this, a retrospective study limits one to the sequences done at the time of investigation and thus inhibits standardisation of the image sequences and image quality. Although we tried to minimise this as much as possible by restricting studies to the last ten years, both factors affecting the reviewers’ diagnostic decision,
The nature, frequency and natural history of intracranial cavernous malformations in adults are outside our control. In a prospective study all suspected cavernous malformations would undergo an agreed protocol of sequences, on an identical scanner, and all suspected cases would be included. As long as a true diagnosis could be reached in all cases, the non-cavernous malformations would be ideal mimics. In this study, mimics also had to be selected retrospectively, which encountered the same disadvantages as the real cases. An added hindrance was their subjective selection, allowing us to make them as easy or as difficult as we liked. Clearly, this could alter the results in either direction. In reality we tried to make them as reasonable and realistic as possible but, unfortunately, we could not avoid subjective methods of selection. As is evident from table 25 a disproportionate number of our mimics were spontaneous haematomas. Clearly follow-up imaging would be likely to clarify the true diagnosis. These were predominantly the cases that lead to the maybe group as an answer. Figures 20 and 21 are examples of images from the study. Figure 20 is a haematoma with an underlying cavernous malformation and figure 21 is a spontaneous haematoma without an underlying CM. The similarity of these images illustrate the limitations of basic sequences at a single point in time. This clinical scenario is faced by radiologists all the time and it explains why further, delayed imaging is often sought. As the haematoma contracts and reorganises an underlying abnormality will become visible. This gives further credence to our arbitrary decision to assume reviewers would have got the correct diagnosis if they had further follow-up imaging available.
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Figure 20 Spontaneous haemorrhage in a cavernoma.

Figure 21 Spontaneous haemorrhage without an underlying cavernoma.

Cavernous malformations are a relatively uncommon condition, the incidence being approximately 0.67 (95% CIs, 0.56 to 0.79) per 100,000 adults per year and therefore
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the reality of gathering cases prospectively in sufficient numbers would be almost impossible. With these limitations in mind, while this study is not a gold standard, it does give a valuable estimate of the sensitivity and specificity of a diagnostic tool that is rapidly overtaking other modalities as the investigation of choice for lesions such as brain cavernous malformations. Our results also go part way towards justifying the use of MR as a screening tool in relatives of those afflicted with the familial form of cavernous malformation.

With advances in technology the multiple functions or sequences of MR scanners are developing faster than we can rationalise what sequences are best for what conditions. Protocols are constantly being refined to the most suitable regime to aid a diagnosis. Therefore it is important to have an indication of the possible diagnosis prior to the investigation. It is not practicable, or necessary, to do all sequences on all patients. Recently in the literature it has been suggested that gradient echo sequences are now an integral part of a basic investigation for a cavernoma. In our study, however, we were surprised to find that only seven out of twenty-eight possible cases had this done. Gradient echo (GRE) was a popular request by the neuroradiologists in the maybe group and, perhaps, a study of this kind should be repeated with and without GRE sequences (see Table 31).

In conclusion, while MR has some limitations (imperfect sensitivity) as a diagnostic tool, in the real world it is a valid screening tool for familial cavernomas and also as
The nature, frequency and natural history of intracranial cavernous malformations in adults

a diagnostic tool for inclusion in studies such as SIVMS. Users need to bear in mind however the importance of informing the radiologists supervising the studies of the potential diagnosis as sequences performed during the scan will be tailored accordingly and will likely have a significant effect on how useful the study will be as a diagnostic tool.
Chapter 9:

Conclusion and future
9.1 Conclusion

My systematic literature review supported my, and the SIVMS steering committee, view that there was little high quality evidence in the public arena on the epidemiology and natural history of intracranial cavernous malformations in adults. The setting up of SIVMS as the first prospective, population-based study of an inception cohort has changed this completely. The robust study design has facilitated this thesis by providing an excellent cohort of patients in whom I could study the epidemiology, presentation and untreated clinical course of this disease. This has not been done before.

This thesis does not answer all questions about intracranial cavernomas. In fact, it highlights some areas where improvements could be made by refining our clinical event definitions. It also suggests trends in the data not anticipated and that cannot be conclusively studied just now, but are important trends to monitor over time as this cohort of patients continues to be followed up, and added to with prospective data from other studies in an individual patient data meta-analysis.

We live in a world where clinical practice is, rightly, more and more dependent on evidence based medicine. This practice also provides patients with accessible information allowing them to be closely involved in decisions about their own treatment. The validity of MR imaging study fills a vacuum in this evidence base in terms of why clinicians now turn to MR as a diagnostic and screening tool for
The nature, frequency and natural history of intracranial cavernous malformations in adults

intraparenchymal cavernomas. Reliance on evidence rather than hunches supporting a
clinician’s practice is a standard that patients expect from their clinicians today.

The salient conclusions for intracranial cavernous malformations in adults arising
from this thesis are

- An estimated incidence of 0.67 (95% CIs, 0.56 to 0.79) per 100,000 adults per
  year
- For a population the size of Scotland, approximately 5.2 million, our results
  predict that approximately twenty-nine new cases of brain cavernomas in
  adults are diagnosed each year.
- The incidence of asymptomatic cavernomas is only slightly less than
  symptomatic CMs, with overlapping confidence intervals - 0.24 (95% CIs,
  0.24 to 0.4) versus 0.36 (95% CIs, 0.28 to 0.45) per 100,000 adults per year.
- Asymptomatic cavernomas present on average a decade later than
  symptomatic cavernomas. They do not appear to have a more benign clinical
  course after diagnosis however.
- The modes of presentation in a population in decreasing order of frequency
  are; asymptomatic (47%), epilepsy (25%), FND (15%) and
  haemorrhage (13%)
- Women are more likely to present with haemorrhage or focal neurological
  deficit (FND)
The nature, frequency and natural history of intracranial cavernous malformations in adults

- Presentation with haemorrhage or FND predicts a poorer outcome in terms of more haemorrhage or FND during follow-up
- Women also have a poorer outcome in terms of more haemorrhage or FND during follow-up
- MR imaging is a valid diagnostic tool for cavernomas although it is still less perfect than the gold standard of histopathology. Its precision would be improved by tailoring of sequences and appropriate timing of scans.

Interesting trends in the data

- Haemorrhages and FNDs appear to cluster in the 2 to 3 years after presentation

9.2 The future

This established cohort of patients has been continuously, prospectively followed-up even since my term as the SIVMS Research Fellow finished. While I have analysed the presentation and early follow-up of these patients, it will be very exciting to see the results of longer term follow-up on the cohort. In particular the trend emerging in my data of a clustering of events in the early post presentation period will be better assessed with more lengthy follow-up.

SIVMS, with it’s robust study design, could serve as a prototype for other studies of the natural history of intracranial cavernomas. Unpicking the overlap between the
The nature, frequency and natural history of intracranial cavernous malformations in adults

clinical events ‘haemorrhage’ and ‘FND’ by refining our definition of FND into ‘non haemorrhagic focal neurological deficit’ and ‘focal neurological deficit not otherwise specified’ as discussed in Chapter 5 would improve the quality of the data. Using these very clear, refined outcome definitions [Al-Shahi, 2008] would facilitate future sensitivity analysis within SIVMS and also between SIVMS and other studies adopting the same approach.

My hope for the future is that once sound evidence of the untreated clinical course of these patients is established, then the research community will turn their attention towards identifying the subgroup of patients who would benefit from treatment. One never knows, perhaps a randomised controlled trial will happen!
Bibliography


The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults

Becker H, Becker H. [Intracerebral hemorrhage misjudged as tumor]. [German]. 


Berry RG, Alpers BJ, and White JC. The site, structure and frequency of intracranial aneurysms, angiomas and arteriovenous abnormalities. Research publications. Association for research in Nervous and Mental Disease. 41, 4-72. 1966.


The nature, frequency and natural history of intracranial cavernous malformations in adults

Bradley WG. MR appearance of haemorrhage in the brain. 


The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults

Denier C, Labarge P, Brunereau L, Cave-Riant F, Marchelli F, Arnoult M et al.


The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults


Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA 1999;282:36-9.


The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults


National Stroke Strategy, 2007 Dec, Department of Health Guidance; Gateway ref 9025:Pg 83. (www.dh.gov.uk)


The nature, frequency and natural history of intracranial cavernous malformations in adults

Numaguchi Y, Fukui M, Miyake E, Kishikawa T, Ikeda J, Matsuura K et al.


Improved preoperative evaluation of cerebral cavernomas by high-field, high-resolution susceptibility-weighted magnetic resonance imaging at 3 Tesla: comparison with standard (1.5 T) magnetic resonance imaging and correlation with histopathological findings--preliminary results. Invest Radiol. 2007;42:346-51.


The nature, frequency and natural history of intracranial cavernous malformations in adults


Bibliography
The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults


The nature, frequency and natural history of intracranial cavernous malformations in adults

Sahoo T, Johnson EW, Thomas JW, Kuehl PM, Jones TL, Dokken CG et al.

Sahoo T, Goenaga-Diaz E, Serebriiskii IG, Thomas JW, Kotova E, Cuellar et al.


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The nature, frequency and natural history of intracranial cavernous malformations in adults


### Appendices

**Appendix 1**

**The five reviewing consultant neuroradiologists from England and Wales**

<table>
<thead>
<tr>
<th>Hospital base</th>
<th>Neuroradiologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkinson Morley’s Hospital, London</td>
<td>A Clifton</td>
</tr>
<tr>
<td>Newcastle General Hospital, Newcastle upon Tyne</td>
<td>A Gholkar</td>
</tr>
<tr>
<td>University Hospital of Wales, Cardiff</td>
<td>S Halpin</td>
</tr>
<tr>
<td>Radcliffe Infirmary, Oxford</td>
<td>A Molyneux</td>
</tr>
<tr>
<td>Newcastle General Hospital, Newcastle upon Tyne</td>
<td>C Soh</td>
</tr>
</tbody>
</table>
Appendix 2

9 December, 2011

Dear <gptitle> «gpsurname»

Re. «patientName», DoB «patdob»
«PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

We are about to contact «patTitle» «patSurname», whom you kindly put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are writing to ask you to check the accuracy of the information we have, and ensure that «patTitle» «patSurname» is still alive and aware of her diagnosis. Please could you also indicate whether it is appropriate to approach her by post and whether you are happy for us to have access to her GP records for the purpose of this research project only?

SIVMS is a prospective, observational study of all patients in Scotland diagnosed with any type of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register all patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals’ medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 97% agree to participate and complete annual questionnaires. We will be sending the patient’s GP a very brief annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. Patient confidentiality will be respected at all times.

We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

Would you please complete the enclosed five-step form and return it to us at your earliest convenience in the freepost envelope supplied. We enclose a copy of the study protocol. Do not hesitate to contact us at the number above if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

Appendices 2
The nature, frequency and natural history of intracranial cavernous malformations in adults

Patient name «patientName»
Date of birth «PatDOB»
Patient address «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»
IVM type «IVMType»
Date of first diagnosis 07/03/02

Please tick (3) appropriate box
Yes No

«patientName» is still alive

He is aware of his diagnosis of an IVM (as above)

I agree to grant access to his GP records for the purpose of this research project

It is appropriate to send him a postal consent form, if his consultant also approves

if 'No', please comment:

..........................................................................................................................................................

Signature __________________________ Date __________________
«gpName» «GPFirstName» «GAPAddress1» «GAPAddress2» «GPCity» «GPRRegion» «GPPPostCode»

Please return this form in the freepost envelope provided to: SNVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Appendices 3
9 December, 2011

Dear [GPTitle] [GPSurname]

Re. [patientName] [PatAddress1] [PatAddress2] [PatAddress3] [PatCity] [PatPostCode]

We would like to contact [PatTitle] [PatSurname], who has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are often told about new cases by Radiologists, so you may receive this letter before seeing the imaging report or hospital correspondence. We are writing to ask if you would kindly check the accuracy of the information we have been supplied with and that [PatTitle] [PatSurname] is still alive and aware of his diagnosis. Please could you also indicate whether it is appropriate to approach him by post and whether you are happy for us to have access to his GP records for the purpose of this research project only (we are happy to discuss remuneration)?

SIVMS is a prospective, observational study of all patients in Scotland with any type of intracranial vascular malformation (IVM). The study is based in all four Scottish Neuroscience centres and our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register all patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We would like to send you a very brief annual questionnaire to collect vital follow-up information about [patientName] that may only be known to you. If the patient is still alive and appropriate for continued follow-up, they will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. For your interest, the protocol is enclosed.

Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

We would be very grateful if you could complete the enclosed five-step form and return it to us in the freepost envelope supplied. You are likely to receive a few letters from us in the near future, but there will only be annual contact thereafter. Do contact us if you have any questions.

Yours Sincerely,

[Dr Julie Hall]
Research Fellow

[Prof Charles P Warlow]
Professor of Medical Neurology
The nature, frequency and natural history of intracranial cavernous malformations in adults

Patient name
Date of birth
Patient address
Patient name is still alive
He is aware of his diagnosis of an IVM (as above)
I agree to grant access to his GP records for the purpose of this research project
It is appropriate to send him a postal consent form, if his consultant also approves
if 'No', please comment:

Signature ___________________________ Date ________________

gpName
GPpracticeName
GPAddress1
GPAddress2
GPCity
GPRregion
GPPostCode

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Appendices 5
9 December, 2011

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
«PatAddress1» «PatAddress2» «PatAddress3», «PatCity» «PatPostCode»

Thank you very much for letting us know about «PatTitle» «PatSurname»’s recent diagnosis of an intracranial vascular malformation (IVM). We are writing to ask you to check the accuracy of the information we have, and ensure that «PatTitle» «PatSurname» is still alive and aware of her diagnosis. Please could you also indicate whether it is appropriate to approach her by post and whether you are happy for us to have access to her hospital records for the purpose of this research project?

SIVMS is a prospective, observational study of all patients in Scotland diagnosed with any type of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register all patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals’ medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrollment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We will be sending the patient’s GP a very brief annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

Would you please complete the enclosed five-step form and return it to us at your earliest convenience in the freepost envelope supplied. Do not hesitate to contact us if you have any further questions.

Yours Sincerely,

Dr Julie Hall
Research Fellow

Prof Charles P Warlow
Professor of Medical Neurology
The nature, frequency and natural history of intracranial cavernous malformations in adults

Patient name  «patientName»
Date of birth  «PatDOB»
Patient address  «PatAddress1»
               «PatAddress2»
               «PatAddress3»
               «PatCity»
               «PatPostCode»
IVM type  «IVMType»
Date of first diagnosis  22/11/00

Please tick (3) appropriate box
Yes  No

«PatTitle» «PatSurname» is still alive

She is aware of her diagnosis of an IVM (as above)

I agree to grant access to her hospital records for the purpose of this research project

It is appropriate to send her a postal consent form, if her GP also approves

If 'No', please comment:

...........................................................................................................................................

Signature  ___________________________ Date  ___________________________

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Appendices  7
9 December, 2011

Dear (patientName) (Surname)

Re. (patientName) (PatAddress1) (PatAddress2) (PatAddress3) (PatCity) (PatPostCode)

(PatTitle) (Surname) under your care has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are writing to ask you to check the accuracy of the information we have been supplied with, and ensure that (PatTitle) (Surname) is still alive and aware of his diagnosis. Please could you also indicate whether it is appropriate to approach him by post and whether you are happy for us to have access to his hospital records for the purpose of this research project?

SIVMS is a prospective, observational study of all patients in Scotland diagnosed with any type of intracranial vascular malformation (IVM) after 1 January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register all patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals’ medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We will be sending the patient’s GP a very brief annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. Patient confidentiality will be respected at all times.

We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

Would you please complete the enclosed five-step form and return it to us at your earliest convenience in the freepost envelope supplied. Do not hesitate to contact us if you have any further questions.

Yours Sincerely,

[Signatures]

Dr Julie Hall
Research Fellow

Prof Charles P Warlow
Professor of Medical Neurology

Appendices 8
The nature, frequency and natural history of intracranial cavernous malformations in adults

Patient name  «patientName»
Date of birth  «PatDOB»
Patient address  «PatAddress1»
               «PatAddress2»
               «PatAddress3»
               «PatCity»
               «PatPostCode»
IVM type  «IVMType»
Date of first diagnosis  07/03/02

Please tick (3) appropriate box
Yes  No

«PatTitle» «PatSurname» is still alive

He is aware of his diagnosis of an IVM (as above)

I agree to grant access to his hospital records for the purpose of this research project

It is appropriate to send him a postal consent form, if his GP also approves

if ‘No’, please comment:
................................................................................................................

Signature  _______________________________ Date  ________________

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU
Appendix 4

9 December, 2011

Dear <GPTitle> <GPSurname>

Re. <patientName>

We wrote to you on <PatGPLetterDate> about <PatTitle> <PatSurname>‘s eligibility for the Scottish Intracranial Vascular Malformation Study (copy enclosed). We are sorry if your reply crosses this reminder in the post and understand if it has not been possible for you to reply to our letter sooner. If you have not already done so, we would be very grateful if you could complete the enclosed form and return it to us at your earliest convenience using the freepost envelope supplied. Do contact us if you have any questions or comments.

Yours Sincerely,

Dr Julie Hall
Research Fellow

Prof Charles P Warlow
Professor of Medical Neurology
9 December, 2011

Dear «CollTitle» «CollSurname»

Re. «patientName»

We wrote to you on «PatConsultantLetterDate» about «PatTitle» «PatSurname»'s eligibility for the Scottish Intracranial Vascular Malformation Study (copy enclosed). We are sorry if your reply crosses this reminder in the post and understand if it has not been possible for you to reply to our letter sooner. If you have not already done so, we would be very grateful if you could complete the enclosed form and return it to us at your earliest convenience using the freepost envelope supplied. Do not hesitate to contact us if you have any questions or comments.

Yours Sincerely,

Dr Julie Hall  
Research Fellow  
Prof Charles P Warlow  
Professor of Medical Neurology

9 triaddevphalaxvateriskenrolment/consultantreminder2.doc SVMS No. «PatID»
The nature, frequency and natural history of intracranial cavernous malformations in adults

Appendix 5

The issue of obtaining a patient’s notes without their explicit consent has arisen on several occasions during our study. We have taken it very seriously, and thought about the issue hard. As a disease register, our access to patient-identifiable information (usually with patients consent, but sometimes without it) is supported by:

1. Approval of our methods by the Multicentre Research Ethics Committee for Scotland (MREC/08/0/488)
   The MREC supports our view that it is in the interest of patients with intracranial vascular malformations (IVMs) that unbiased population-based disease registers ascertain their long-term prognosis. This can only be done with a representative sample of patients. If patients who are unable to explicitly consent to our purely observational study are excluded (be they dead, anxious, cognitively impaired or otherwise) then we will arrive at the wrong conclusion, and seriously underestimate the morbidity and mortality associated with IVMs. We respect confidentiality enormously, and keep all electronic data within a password-protected database, and notes within locked filing cabinets in a locked room, in a locked department.

2. Updated guidance from the GMC (Research: the role and responsibilities of doctors, February 2002, paragraph 34)
   Where it is not practicable to contact participants to seek their consent to the anonymisation of data or use of identifiable data in research, this fact should be drawn to the attention of a research ethics committee so that it can consider whether the likely benefits of the research outweigh the loss of confidentiality to the patient.

3. The Confidentiality and Security Advisory Group for Scotland’s (CSAGS) Report to Scottish Ministers (paragraph 7.17)
   CSAGS was given the task of addressing the legal, ethical and professional requirements on confidentiality in NHS Scotland. A large number of clinicians – including our Steering Committee – responded to the initial consultation document. Their document states: “Our initial view was that explicit consent would be the requirement, based on the ethical premise that patients have a right to know about the use of their personal health data (both) with their treatment needs and a right to withhold consent for such uses. That ideal remains best practice and our expectation is that it should become normal practice as better-informed patients share in future decisions about use of their data. However, we have found the arguments in favour of permitting implied consent for [disease registers] persuasive, i.e. to safeguard valuable data for the future of services and the improvement of the health of the population.”

4. The patients participating in the study
   Of the patients we have been allowed to approach for their consent in the first two years of the study, only 2.5% of those returning their consent form did not wish to participate in the study.

For these reasons, I wonder whether you would kindly reconsider whether we could access the case notes without explicit consent, in these particular circumstances?

Yours sincerely

Dr Julie Hall
Research Fellow
Appendix 6

9 December 2011

«GPForename» «GPSurname»
«GPPName»
«GPAddress1»
«GPAddress2»
«GPCity», «GPPostCode»

Dear «GPForename» «GPSurname»

Re. «name», «PatAddress1», «PatAddress2», «PatAddress3»
«PatCity», «PatPostCode» Date of birth «PatDOB»

Thank you for replying to our last letter about «PatTitle» «PatSurname» on «PatGPLetterResponse».

We are sorry to have to bother you about our study again, but we would be grateful for your help to avoid “cold-calling” «PatTitle» «PatSurname» ourselves, yet obtain her consent to join our study to gain important information about the prognosis and treatment of her condition.

All we are asking you to do is to sign the enclosed letter from yourself to «PatTitle» «PatSurname», unless you wish to re-draft it, and post it with the enclosed package to her in the pre-paid envelope provided. The forms and pre-paid envelope are designed to make the task as easy and inexpensive for you as possible.

We are sorry to bother you with what we hope will be a small task. We have been instructed to approach patients in this way by the Multicentre Research Ethics Committee for Scotland. Do contact us if you have any questions or comments.

Thank you in advance for your support.

Yours Sincerely

Dr Julie Hall
Research Fellow

Prof. Charles P. Warlow
Professor of Medical Neurology

Appendices 13
Dear «PatTitle» «PatSurname»

I am writing to you on behalf of Professor Charles Warlow and colleagues in the Department of Clinical Neurosciences at the Western General Hospital in Edinburgh. They are running the Scottish Intracranial Vascular Malformation Study (SIVMS). SIVMS is a medical research study that gathers information about people with any type of intracranial vascular malformation, known as 'IVMs' for short. As a result of your recent tests at the «CentreName», they understand you may be affected by this medical condition.

Please could you read the enclosed information leaflet, which gives further information about the study? If you are willing to take part, I would be very grateful if you would complete the consent form and SIVMS Questionnaire, and return them in the enclosed freepost envelope to the study team in Edinburgh as soon as you can. They would be very pleased if you took part so that we can all find out more about IVMs and how to manage them better.

Thank you in advance for your support of their study.

Yours Sincerely
Appendix 7

<table>
<thead>
<tr>
<th>S I V M S consent form</th>
<th>Please tick (4) appropriate box</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>1. Have you read the information leaflet?</td>
<td></td>
</tr>
<tr>
<td>2. Has the leaflet given you enough information about the study?</td>
<td></td>
</tr>
<tr>
<td>3. Have you been offered an opportunity to ask questions and discuss this study (see leaflet)?</td>
<td></td>
</tr>
<tr>
<td>4. If so, have you received satisfactory answers to your questions?</td>
<td></td>
</tr>
<tr>
<td>5. Do you understand that participation is entirely voluntary?</td>
<td></td>
</tr>
<tr>
<td>6. Do you understand that you are free to withdraw from the study:</td>
<td></td>
</tr>
<tr>
<td>at any time?</td>
<td></td>
</tr>
<tr>
<td>without having to give a reason for withdrawing?</td>
<td></td>
</tr>
<tr>
<td>without this affecting your future medical care?</td>
<td></td>
</tr>
<tr>
<td>Are you happy to receive a short questionnaire once a year?</td>
<td></td>
</tr>
<tr>
<td>Can we have access to your medical records, for the purposes of this study ONLY (we will respect confidentiality at ALL times)?</td>
<td></td>
</tr>
</tbody>
</table>

- Signature: ________________________________ Date: __________________

Assent by another person (if you are unable to complete this form):

- Signature: ________________________________ Date: __________________

Name (capitalized): ________________________________
Relationship to the person named above: ________________________________

Now return this to us in the freepost envelope. Thank you!
The nature, frequency and natural history of intracranial cavernous malformations in adults

### SIVMS Questionnaire

1. Please check the information below and correct it if necessary.
2. Then answer the other questions in the shaded boxes.
3. Ask a friend or relative for assistance if you need it.

| 1 | Your title | «PatTitle» |
|   | Your first name | «PatForename» |
|   | Your middle initials | «PatInitials» |
|   | Your surname | «PatSurname» |
|   | Your date of birth | «PatDOB» |
|   | Your address | «PatAddress1» |
|   | | «PatAddress2» |
|   | Postcode | «PatPostCode» |
|   | Telephone number | «PatTelephone» |
|   | email address | |

2. Who is your next of kin?
   
3. What is their telephone number?
   
4. What is your marital status?
   
5. Are you?  
   - male ☐  go to 6  
   - female ☐  go to 6

6. Maiden name (if applicable)
   
7. How many children have you had?
   
8. Which hand do you write with?  
   - Right ☐  Left ☐  Both ☐

9. What is your ethnic origin?  
   *(please tick one)*
   - White ☐  Pakistani ☐
   - Black-Caribbean ☐  Bangladeshi ☐
   - Black-African ☐  Chinese ☐
   - Black-other ☐  Indian ☐
   - Other ☐

*Please go to page 2...*
The nature, frequency and natural history of intracranial cavernous malformations in adults

### SIVMS Questionnaire

**Page 2**

1. Please check the information below and correct it if necessary.
2. Then answer the other questions in the shaded boxes.
3. Ask a friend or relative for assistance if you need it.

| 10 | We have been told you have | «IVMType» |
| 11 | It was first diagnosed on | «PatDiagnosisDate» |
| 12 | You are looked after for this by | «collName» |
| | at the following hospital | «CentreName» |
| 13 | Your General Practitioner is | «gpName» |
| | «GPPacticeName» |
| | «GPAddress1» «GPAddress2» |
| | «GPCity» «GPPostCode» |

| 14 | Please list any other medical problems you may have |
| |  |

| 15 | Please list any pills, tablets or other treatments you are taking |
| |  |

| 16 | Has anyone in your family had a brain haemorrhage, epilepsy or an abnormal tangle of blood vessels in their brain like yours? |
| | Please tick one box (and give details if “Yes”). |
| | Yes □ |
| | No □ |

| 17 | Is there anything else that you think we should know, or that you would like to add? |
| |  |

*Now return this to us in the freepost envelope. Thank you!*

Appendices 17
Who organises and funds the research?

This study is sponsored by the UK Medical Research Council and the Chief Scientist Office of the Scottish Executive. The research team is based in Edinburgh, but the study is overseen by a Steering Committee with representatives from all over Scotland.

How can I obtain more information?

In this leaflet we have attempted to give you information on the scientific and ethical background of the study. Please contact the SIVMS team if you have any concerns about registration, if you want further information about IVMs, or if you decide to withdraw from the study.

For further information...
If you would like more information about any type of IVM, please contact us by telephone, fax, post or e-mail (details overleaf).
You may also seek advice about SIVMS from your hospital consultant or an independent adviser (see below).

Independent adviser
Professor Peter Sanderson is available for independent advice about this study at the address overleaf, or by telephoning 0131 537 2828.
The nature, frequency and natural history of intracranial cavernous malformations in adults

Appendices

Why have I been chosen?

One of the doctors involved in your care has told us that you have a type of 'intracranial vascular malformation', or 'IVM'. An IVM is a tangle of blood vessels in your brain. The different types of IVM are:

- Arteriovenous malformation (AVM)
- Cavernous malformation ('cavernoma' or 'cavernous angiomata')
- Venous malformation ('venous anomaly')
- Dural arteriovenous fistula

So that we can find out more about these rare, but important conditions, we invite you to participate in 'SIVMS', the Scottish Intracranial Vascular Malformation Study.

What is the purpose of the study?

The aim of SIVMS is to find every person with an IVM in Scotland and enroll them in a confidential register. We only ask for a few minutes of your time each year.

Why do we need a register?

We are using the register to:
1. Find out how common IVMs are in Scotland
2. Find out what is important to you about having an IVM
3. Understand better the particular problems caused by IVMs over time

A large print version of this leaflet can be supplied

What will happen if I take part?

After you register, we will extract some basic information about your medical history from your medical records. If you agree, we will also send you a short questionnaire asking some simple questions about your day-to-day life. This should take only 20 minutes to complete. We may occasionally need to telephone you.

We need to find out what happens to people with your condition over long periods of time, and not just in the short term. Therefore we will need to look at your medical records from time to time. We would also like to send you a questionnaire every year, if appropriate, for the rest of your life.

If English is not your first language, this leaflet could be translated for you

Will the information be confidential?

Any information collected about you will be kept strictly confidential and used only for this study. These details will only be available to research staff, and no one else. The published results of the research will not identify individual people. We comply with the Data Protection Act 1998. We have full ethical approval for this study from the Multi-centre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

We assure you complete confidentiality

Do I have to take part?

It is up to you to decide whether or not to take part. Please complete and sign the enclosed registration and consent forms to let us know what your decision is. If it helps, ask a friend or relative to fill in the forms for you. Please keep this information leaflet and a copy of the consent form for your records.

If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw or not to take part will not affect the standard of care you receive.

Thank you for taking time to read this information leaflet. Please keep it in a safe place for future reference
9 December, 2011

Dear GPTitle «GPInitials» «GPSurname»

Re. «PatTitle» «PatForename» «PatInitials» «PatSurname» «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

It is now approximately one year since «PatTitle» «PatSurname» was last contacted about the Scottish Intracranial Vascular Malformation Study (SIVMS).

Because we are about to send her a follow-up questionnaire, we would be very grateful to you for checking the details on the attached sheet. Although we do follow-up «PatTitle» «PatSurname» through her hospital notes, there is vital follow-up information that only you will be able to help us with.

For this reason, we have also enclosed a letter asking for copies of recent records held in her GP notes relating to this follow-up information.

We would therefore be very grateful if you could please check the details on the attached sheet and return the seven-step form with the relevant copies of her GP notes, if appropriate, to us in the freepost envelope provided.

We enclose a pad of post-its and a yearly GP newsletter, as a small token of our gratitude to you for helping with the study.

Yours Sincerely

Dr Julie Hall
Research Fellow

Prof Charles P Warlow
Professor of Medical Neurology

Appendices 20
The nature, frequency and natural history of intracranial cavernous malformations in adults

Patient name «PatName» «PatSurname» «PatTitle» «PatForename» «PatInitiates»
Date of birth «PatDOB»
Patient address «PatAddress1», «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

Please tick (i) appropriate box
Yes No

is «PatTitle» «PatSurname» still alive?
If you answered ‘No’, please tell us her date of death:

is her address the same (as above)?
If you answered ‘No’, please amend the address.

«PatTitle» «PatSurname» agreed to complete an annual questionnaire.
Is it still appropriate to send her a questionnaire?
If you answered ‘No’, please comment:

Has «PatTitle» «PatSurname» been seen about her intracranial vascular malformation in hospital in the last year?
If you answered ‘Yes’, please fill in this section:

<table>
<thead>
<tr>
<th>Approximate date of hospital visit / stay</th>
<th>Which hospital?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consultant (if known) Reason for appointment / admission

please continue overleaf if necessary

If not already mentioned in |, has «PatTitle» «PatSurname» suffered from the following in the last year (giving date(s) where applicable)?

Brain haemorrhage(s) Yes / No day/mouth/year

Epilepsy Yes / No day/mouth/year

Which of these best describes «PatTitle» «PatSurname»’s current state?

No symptoms
Minor symptoms, which do not interfere with her lifestyle
Some restrictions to her lifestyle, but she looks after herself

Significant restriction to lifestyle, preventing total independence
Severe handicap preventing independent existence, but not requiring constant attention
Severe handicap, totally dependent, requiring attention night and day

Signature «GPName» «GSPName»
«GPPracticeName» «GPAddress1», «GPAddress2» «GPPostCode»

Date day/mouth/year

Please return this form in the freepost envelope to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Appendices 21
Appendix 9

9 December, 2011

Dear «GPFirstName» «GPInitials» «GPSurname»,

Re. «PatFirstName» «PatInitials» «PatSurname»

We wrote to you on «AGSentDate» about «PatFirstName» «PatSurname»'s participation in the Scottish Intracranial Vascular Malformation Study (copy enclosed). We are sorry if your reply crosses this reminder in the post and understand if it has not been possible for you to reply to our letter sooner.

If you have not already done so, we would be very grateful if you could complete the enclosed form and return it to us at your earliest convenience using the freepost envelope supplied. Although we do follow-up «PatFirstName» «PatSurname» through her hospital notes, there is vital follow-up information that only you will be able to help us with. Do not hesitate to contact us at the number above if you have any questions or comments.

Yours Sincerely,

Dr Julie Hall
Research Fellow

Prof Charles P Warlow
Professor of Medical Neurology

Appendices 22
The nature, frequency and natural history of intracranial cavernous malformations in adults

Patient name «PatTitle» «PatForename» «PatSurname»
Date of birth «PatDOB»
Patient address «PatAddress1», «PatAddress2»
«PatAddress3» «PatCity» «PatPostCode»

Please tick (4) appropriate box
Yes ☐ No ☐

is «PatTitle» «PatSurname» still alive?
If you answered 'No', please tell us her date of death:
☐ ☐

is her address the same (as above)?
If you answered 'No', please amend the address:
☐ ☐

«PatTitle» «PatSurname» agreed to complete an annual questionnaire.
Is it still appropriate to send her a questionnaire?
If you answered 'No', please comment:
☐ ☐

Has «PatTitle» «PatSurname» been seen about her intracranial vascular malformation in hospital in the last year?
If you answered 'Yes', please fill in this section:
☐ ☐

Approximate date of hospital visit / stay
Which hospital?
Consultant (if known)
Reason for appointment / admission

☐ ☐ ☐ ☐ ☐ ☐

If not already mentioned in ☐ ☐, has «PatTitle» «PatSurname» suffered from the following in the last year (giving date(s) where applicable)?

Brain haemorrhage(s) Yes / No day/month/year
Epilepsy Yes / No day/month/year

Which of these best describes «PatTitle» «PatSurname»'s current state?
☐ ☐ ☐ ☐ ☐
No symptoms
Minor symptoms, which do not interfere with her lifestyle
Some restrictions to her lifestyle, but she looks after herself
Significant restriction to lifestyle, preventing total independence
Severe handicap preventing independent existence, but not requiring constant attention
Severe handicap, totally dependent, requiring attention night and day

Signature «GPTtitle» «GPSurname»
«GPTpracticeName»
«GPAaddress1», «GPAaddress2»
«GPOcity» «GPOpostcode»

Please return this form in the freepost envelope to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

copy
Appendices 23
Appendix 10

SIVMS Yearly Questionnaire

Your Title: Mr
Your First Name: [Redacted]
Your Middle Initials: [Redacted]
Your Surname: [Redacted]
Your Address: Livingston West Lothian
Post Code: EH54 8PD
Telephone number: [Redacted]
SIVMS number: [Redacted]

Please correct your details, if necessary

Instructions for completing the questionnaire

1. Please answer every question.
2. Some questions may look a bit like others, but each one is different.
3. Please take time to read each question carefully, and tick the box next to the answer that is closest to the way you feel.
4. Ask a friend or relative for help if you need it.
5. Return your completed questionnaire in the freepost envelope provided.
6. Please turn the page and begin answering the questions now.
The nature, frequency and natural history of intracranial cavernous malformations in adults

1. Please read the following descriptions from people who have had similar medical problems to you and choose one which best describes your present state:

   - I have no problems at all and cope well with life.  
   - I have a few symptoms but these do not interfere with my everyday life.  
   - I have symptoms which have caused some changes in my life, but I am still able to look after myself.  
   - I have symptoms which have significantly changed my life and prevent me from coping fully, and I need some help with looking after myself.  
   - I have quite severe symptoms which mean I need to have help from other people, but I am not so bad as to need attention day and night.  
   - I have major symptoms which severely handicap me and I need constant attention day and night.

2. In general would you say your health is:

   - Tick one box
   - Excellent
   - Very good
   - Good
   - Fair
   - Poor

3. Compared to one year ago, how would you rate your health in general now?

   - Tick one box
   - Much better than one year ago
   - Somewhat better than one year ago
   - About the same
   - Somewhat worse now than one year ago
   - Much worse now than one year ago
4. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Vigorous activities, such as running, lifting heavy objects,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>participating in strenuous sports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Moderate activities, such as moving a table, pushing a vacuum cleaner,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bowling or playing golf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Lifting or carrying groceries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Climbing several flights of stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Climbing one flight of stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f) Bending, kneeling or stooping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g) Walking more than a mile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h) Walking half a mile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Walking 100 yards</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>j) Bathing and dressing yourself</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>Problem</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were limited in the kind of work or other activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had difficulty performing the work or other activities (for example, it</td>
<td></td>
<td></td>
</tr>
<tr>
<td>took extra effort)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please turn the page and continue...
6. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down on the <strong>amount of time</strong> you spent on work or other activities</td>
<td></td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td></td>
</tr>
<tr>
<td>Didn’t do work or other activities as <strong>carefully as usual</strong></td>
<td></td>
</tr>
</tbody>
</table>

7. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

<table>
<thead>
<tr>
<th>Tick one box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
</tr>
<tr>
<td>Slightly</td>
</tr>
<tr>
<td>Moderately</td>
</tr>
<tr>
<td>Quite a bit</td>
</tr>
<tr>
<td>Extremely</td>
</tr>
</tbody>
</table>

8. How much **bodily pain** have you had during the **past 4 weeks**?

<table>
<thead>
<tr>
<th>Tick one box</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>Very mild</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Very severe</td>
</tr>
</tbody>
</table>

9. During the **past 4 weeks**, how much did **pain** interfere with your normal work (both outside the home and housework)?

<table>
<thead>
<tr>
<th>Tick one box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
</tr>
<tr>
<td>A little bit</td>
</tr>
<tr>
<td>Moderately</td>
</tr>
<tr>
<td>Quite a bit</td>
</tr>
<tr>
<td>Extremely</td>
</tr>
</tbody>
</table>
The nature, frequency and natural history of intracranial cavernous malformations in adults

10. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please indicate the one answer that comes closest to the way you have been feeling. How much during the past 4 weeks:

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Did you feel full of life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Have you been a very nervous person?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Have you felt so down in the dumps that nothing could cheer you up?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Have you felt calm and peaceful?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Did you have a lot of energy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f) Have you felt downhearted and low?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g) Did you feel worn out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h) Have you been a happy person?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Did you feel tired?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends or close relatives)?

Tick one box

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

Please turn the page and continue...
The nature, frequency and natural history of intracranial cavernous malformations in adults

12. How TRUE or FALSE is each of the following statements for you:

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>I seem to get ill more easily than other people</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am as healthy as anybody I know</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I expect my health to get worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My health is excellent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13. In the past week did you have full control of your bowels most days?

Tick one box

Yes [ ]
No, I have occasional accidents (once a week) [ ]
No, I am incontinent or need help with an enema [ ]

14. In the past week did you have full control of your bladder most days?

Tick one box

Yes [ ]
No, I have occasional accidents (less than once a day) [ ]
No, I am incontinent (or use a catheter) [ ]

15. In the last two days did you manage to clean your teeth, brush your hair or shave without help?

Tick one box

Yes [ ]
No, I need help [ ]

16. In the past two weeks could you use the toilet (or commode) without help from another person?

Tick one box

Yes, I am independent [ ]
No, I need minor assistance [ ]
No, I need quite a lot of help [ ]
17. In the last two weeks did you need help from another person to eat meals?

Tick one box

No, I am independent
Yes, I need some help
Yes, I need quite a lot of help

18. In the past two weeks did you need help from another person to get out of bed or up from a chair?

Tick one box

No, I am totally independent
Yes, I need minimal help
Yes, I can sit unaided, but I need help to transfer
Yes, I am unable to transfer

19. In the past two weeks did you need help from another person with walking?

Tick one box

No, I am independent for at least 50 yards
Yes, I can walk 50 yards with help
I am independent in a wheelchair for 50 yards
Yes, I am immobile

20. In the last two weeks did you need help from another person to dress and undress?

Tick one box

No, I am independent
Yes, I need help with some things
Yes, I need help with most things

21. In the past two weeks did you need help from another person to climb stairs?

Tick one box

No, I am independent
Yes, I need physical help or verbal support
I am unable

Please turn the page and continue…
22. **In the last two weeks did you manage to have a bath, shower or wash all over without help?**

   Tick one box
   
   Yes [ ]
   No, I need help [ ]

23. **I feel tense or ‘wound up’:**

   Tick one box
   
   Most of the time [ ]
   A lot of the time [ ]
   From time to time, occasionally [ ]
   Not at all [ ]

24. **I still enjoy the things I used to enjoy:**

   Tick one box
   
   Definitely as much [ ]
   Not quite so much [ ]
   Only a little [ ]
   Hardly at all [ ]

25. **I get a sort of frightened feeling as if something awful is about to happen:**

   Tick one box
   
   Very definitely and quite badly [ ]
   Yes, but not too badly [ ]
   A little, but it doesn’t worry me [ ]
   Not at all [ ]

26. **I can laugh and see the funny side of things:**

   Tick one box
   
   As much as I always could [ ]
   Not quite so much now [ ]
   Definitely not so much now [ ]
   Not at all [ ]
The nature, frequency and natural history of intracranial cavernous malformations in adults

27. Worrying thoughts go through my mind:

Tick one box
A great deal of the time □
A lot of the time □
From time to time, but not too often □
Only occasionally □

28. I feel cheerful

Tick one box
Not at all □
Not often □
Sometimes □
Most of the time □

29. I can sit at ease and feel relaxed:

Tick one box
Definitely □
Usually □
Not often □
Not at all □

30. I feel as if I am slowed down:

Tick one box
Nearly all the time □
Very often □
Sometimes □
Not at all □

31. I get a sort of frightened feeling like “butterflies” in the stomach:

Tick one box
Not at all □
Occasionally □
Quite often □
Very often □

*Please turn the page and continue*...
32. I have lost interest in my appearance:

- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

33. I feel restless as if I have to be on the move:

- Very much indeed
- Quite a lot
- Not very much
- Not at all

34. I look forward with enjoyment to things:

- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

35. I get sudden feelings of panic:

- Very often indeed
- Quite often
- Not very often
- Not at all

36. I can enjoy a good book or radio or TV programme:

- Often
- Sometimes
- Not often
- Very seldom
37. Do you have nose bleeds?
   Yes ☐ If ‘Yes’ go to question 38
   No ☐ If ‘No’ go to question 40

38. At what age did they start?

39. How often do you have nosebleeds?

40. Do you have any red spots on your lips, tongue or fingers?
   Yes ☐ If ‘Yes’ go to question 41
   No ☐ If ‘No’ go to question 43

41. How many red spots do you have?

42. Where are these red spots?

43. Are you now, or have you ever been, significantly bothered by recurrent headaches?

44. Do you have epilepsy (‘seizures’ or ‘fits’)?
   We will not disclose the answer you give to this question to the Driving Vehicle Licensing Authority
   Yes ☐
   No ☐

Please turn the page and continue...
The nature, frequency and natural history of intracranial cavernous malformations in adults

45. Since the last time we contacted you, has anyone in your family developed a brain haemorrhage, epilepsy or an abnormal tangle of blood vessels in their brain like yours?
   □ No
   □ Yes... Please provide details below under question 48

46. Who completed this questionnaire?
   □ You
   □ Someone else... Please state name and relationship to the person named on the front of this form:

47. Signature of the person completing this questionnaire: ____________________________ Date of completion: __________

48. Please add any comments below:

49. Please return this questionnaire to us in the freepost envelope.

THANK YOU FOR YOUR HELP!
Appendix 11

SIVMS Headache Questionnaire

<table>
<thead>
<tr>
<th>Field</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your Title</td>
<td>«PatTitle»</td>
</tr>
<tr>
<td>Your First Name</td>
<td>«PatForename»</td>
</tr>
<tr>
<td>Your Middle Initials</td>
<td>«PatInitials»</td>
</tr>
<tr>
<td>Your Surname</td>
<td>«PatSurname»</td>
</tr>
<tr>
<td>Your Address</td>
<td>«PatAddress1»</td>
</tr>
<tr>
<td></td>
<td>«PatAddress2»</td>
</tr>
<tr>
<td></td>
<td>«PatAddress3»</td>
</tr>
<tr>
<td></td>
<td>«PatCity»</td>
</tr>
<tr>
<td>Post Code</td>
<td>«PatPostCode»</td>
</tr>
<tr>
<td>Telephone number</td>
<td>«PatTelephone»</td>
</tr>
<tr>
<td>SIVMS No.</td>
<td>«PatID»</td>
</tr>
</tbody>
</table>

Please correct your details, if necessary

Instructions for completing the questionnaire

1. Please answer every question.
2. Some questions may look a bit like others, but each one is different.
3. Please take time to read each question carefully, and tick the box next to the answer that is closest to the way you feel.
4. Ask a friend or relative for help if you need it.
5. Return your completed questionnaire in the freepost envelope provided.
6. Please turn the page and begin answering the questions now.
Questionnaire No. «QAnnualGPI»

1. **How often have you had headaches in the past year?**

   Please tick one box
   - Never
   - Less than once per month
   - Once or more per month

2. **Have you had at least 5 separate attacks of headache severe enough to require that you stop or decrease your activities or take a medication for pain?**

   Tick one box
   - Yes
   - No
   
   If ‘No’ stop here.

3. **Do you have headache-free intervals of days to weeks between severe headache attacks?**

   Tick one box
   - Yes
   - No

4. **Do your headache attacks usually last more than four hours and less than three days?**

   Tick one box
   - Yes
   - No
   
   If ‘No’ stop here.

5. **Are your most bothersome headaches:**

   Tick one box on each line
   - Yes
   - No
   - Often pulsating (‘throbbing’)?
   - Often on one side of the head, for at least a portion of the headache attack?
   - Severe enough to make you stop or decrease your activities?
   - Made worse by physical activity?
6. Are your headache attacks accompanied by:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea or vomiting?</td>
<td></td>
</tr>
<tr>
<td>Sensitivity to light?</td>
<td></td>
</tr>
<tr>
<td>Sensitivity to noise?</td>
<td></td>
</tr>
</tbody>
</table>

7. With at least 2 of your headache attacks have you had temporary visual disturbance (for example, shimmering lights, zigzags, blind spots, circles, crescent shapes) just before or during the headache?

<table>
<thead>
<tr>
<th>Tick one box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

If ‘No’ go to question 13

8. Which of the following best describes your visual disturbance:

<table>
<thead>
<tr>
<th>Tick one box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver streaks</td>
</tr>
<tr>
<td>White lights</td>
</tr>
<tr>
<td>Light objects appearing excessively bright</td>
</tr>
<tr>
<td>All objects appearing grey or yellow</td>
</tr>
<tr>
<td>Distortion of all linear objects</td>
</tr>
<tr>
<td>Dancing or moving cobwebs</td>
</tr>
<tr>
<td>Moving black veils</td>
</tr>
<tr>
<td>Scintillating picket fences</td>
</tr>
<tr>
<td>Silver stars</td>
</tr>
</tbody>
</table>

9. Does the visual disturbance go away completely within 60 minutes?

<table>
<thead>
<tr>
<th>Tick one box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

10. How long does the visual disturbance last? __________ minutes

*Please turn the page and continue...*
11. Does the visual disturbance change (for example, get worse or change in character) within 4 minutes?

Tick one box
- Yes ☐
- No ☐

12. Is the visual disturbance associated with headache, nausea, and/or light sensitivity immediately or within 60 minutes?

Tick one box
- Yes ☐
- No ☐

13. With at least 2 of your headache attacks have you had temporary numbness, tingling, or both involving the lips, tongue, fingers or legs, occurring just before or during the headache?

Tick one box
- Yes ☐
- No ☐

14. Have you had headaches accompanied by both visual disturbance and temporary numbness/tingling?

Tick one box
- Yes ☐
- No ☐

15. Who completed this questionnaire?

☐ You
☐ Someone else… Please state name and relationship to the person named on the front of this form:

16. Signature of the person completing this questionnaire:

Date of completion:

17. Please return this questionnaire to us in the freepost envelope.

THANK YOU FOR YOUR HELP!
The nature, frequency and natural history of intracranial cavernous malformations in adults

Appendix 12

SIVMS Epilepsy Questionnaire

<table>
<thead>
<tr>
<th>Field</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your Title</td>
<td>«PatTitle»</td>
</tr>
<tr>
<td>Your First Name</td>
<td>«PatForename»</td>
</tr>
<tr>
<td>Your Middle Initials</td>
<td>«PatInitials»</td>
</tr>
<tr>
<td>Your Surname</td>
<td>«PatSurname»</td>
</tr>
<tr>
<td>Your Address</td>
<td>«PatAddress1»</td>
</tr>
<tr>
<td></td>
<td>«PatAddress2»</td>
</tr>
<tr>
<td></td>
<td>«PatAddress3» «PatCity»</td>
</tr>
<tr>
<td>Post Code</td>
<td>«PatPostCode»</td>
</tr>
<tr>
<td>Telephone number</td>
<td>«PatTelephone»</td>
</tr>
<tr>
<td>SIVMS No.</td>
<td>«PatID»</td>
</tr>
</tbody>
</table>

Please correct your details, if necessary

Instructions for completing the questionnaire

1. Please answer every question.
2. Some questions may look a bit like others, but each one is different.
3. Please take time to read each question carefully, and tick the box next to the answer that is closest to the way you feel.
4. Ask a friend or relative for help if you need it.
5. Return your completed questionnaire in the freepost envelope provided.
6. Please turn the page and begin answering the questions now.
1. Below are some descriptions of different kinds of epileptic attacks. Which of these descriptions matches the attacks you have?

Please tick all the boxes that apply to you

‘Grand mal’ attacks. Unconsciousness with the body becoming stiff with jerking of all the limbs, and frothing at the mouth, possibly with difficulty breathing. Followed by a period of sleepiness and confusion lasting for at least 5 minutes before a full recovery.

‘Petit mal’ attacks. A brief episode of no more than a few seconds with blankness without falling and possibly flickering of the eyelids.

Attacks with a trance-like state, sometimes with lip-smacking, swallowing, gesturing or fidgeting, followed by confusion, usually with at least a minute before full recovery.

Attacks of falling with a brief loss of consciousness preceded by a feeling of light-headedness which comes on gradually, but which may be followed by sweating and clamminess, shakiness and sickness

Brief jerks of the arms and body (sometimes the legs) occurring usually within an hour or two of waking without any blackout

Some other kind of attack
please describe below

2. Do your attacks happen:

Please tick one box

Only while you are asleep

Only while you are awake

At any time of day or night

3. How old were you when you had your first epileptic attack?

\[ \text{\[ \text{years} \]} \]

4. When did you have your last attack?

Please give the date \[ / / \]
5. How many epileptic attacks have you had in the past year?
Please tick one box

- None
- Less than one per month
- One or more per month

6. Who completed this questionnaire?

- You
- Someone else...

Please state name and relationship to the person named on the front of this form:


7. Signature of the person completing this questionnaire: Date of completion:


8. Please return this questionnaire to us in the freepost envelope.

THANK YOU FOR YOUR HELP!
Appendix 13

1. What is the quality of these films?
   - Excellent
   - Good
   - Average
   - Poor
   - Very poor

2. Are there any lesions with imaging characteristics of a cavernoma?
   - Yes
   - No

   If "yes", go to page 2 now.

3. Are there any other lesions (without imaging characteristics of a cavernoma)?
   - Yes
   - No

   If yes, how many?

For each lesion, please provide details of brain side, brain location and type of lesion in the space provided below.
For brain location please use the categories provided in the list at the bottom of the page.

<table>
<thead>
<tr>
<th>Side (please circle one)</th>
<th>Location (choose from list below)</th>
<th>Type of lesion (e.g. glioma, AVM, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. left midline right</td>
<td>1. ______________________________</td>
<td>1. ______________________________</td>
</tr>
<tr>
<td>2. left midline right</td>
<td>2. ______________________________</td>
<td>2. ______________________________</td>
</tr>
<tr>
<td>3. left midline right</td>
<td>3. ______________________________</td>
<td>3. ______________________________</td>
</tr>
<tr>
<td>4. left midline right</td>
<td>4. ______________________________</td>
<td>4. ______________________________</td>
</tr>
</tbody>
</table>

Categories for brain location:
- Frontal
- Temporal
- Frontotemporal
- Temporoparietal
- Frontoparietal
- Occipital
- Temporal
- Parietal
- Parieto-occipital
- Insula
- Basal ganglia
- Hypothalamus
- Thalamus
- Cerebellum
- Brainstem
- Choroidal
- Callosal
- Internal capsule
- Dural
The nature, frequency and natural history of intracranial cavernous malformations in adults

For the first cavernoma-like lesion :-

A On which side of the brain is the lesion located?
   - Left
   - Midline
   - Right

B Which area of the brain is the lesion in? (Please select all that apply)
   - Frontal
   - Frontotemporal
   - Frontoparietal
   - Temporal
   - Temporoparietal
   - Occipital
   - Parietal
   - Parieto-occipital
   - Insula
   - Basal ganglia
   - Hypothalamus
   - Thalamus
   - Brainstem
   - Cerebellum
   - Dural
   - Internal capsule
   - Callosal
   - Choroidal

C Is it definitely a cavernoma?
   - Yes
   - No
   If "yes" go to D

If "no", what would you do to improve certainty?

Either
   At the time of current scan, proceed to perform (please tick all that apply)
   - Proton density weighted imaging
   - Fluid-attenuated inversion recovery imaging
   - T1 weighted imaging + contrast (if not already done)
   - Gradient echo imaging
   - Diffusion weighted imaging
   - MRA
   - Catheter angiography
   - Other (please specify)

or
   Perform a follow-up scan at (please circle)
   1 month  6 months  1 year  >1 year
   with (please tick all that apply)
   - Proton density weighted imaging
   - Fluid-attenuated inversion recovery imaging
   - T1 weighted imaging + contrast
   - Gradient echo imaging
   - Diffusion weighted imaging
   - MRA
   - Catheter angiography
   - Other (please specify)

D If there is another cavernoma-like lesion, go to page 3
If not, go back to page 1 and complete Question 3
The nature, frequency and natural history of intracranial cavernous malformations in adults

For the second cavernoma-like lesion:

**A** On which side of the brain is the lesion located?
- Left
- Midline
- Right

**B** Which area of the brain is the lesion in? (Please select all that apply)
- Frontal
- Frontotemporal
- Frontoparietal
- Temporal
- Temporoparietal
- Occipital
- Parietal
- Parieto-occipital
- Insula
- Basal ganglia
- Hypothalamus
- Thalamic
- Brainstem
- Cerebellum
- Dural
- Internal capsule
- Callosal
- Choroidal

**C** Is it definitely a cavernoma?
- Yes
- No

If "no", what would you do to improve certainty?

Either: At the time of current scan, proceed to perform (please tick all that apply)
- Proton density weighted imaging
- Fluid-attenuated inversion recovery imaging
- T1 weighted imaging + contrast (if not already done)
- Gradient echo imaging
- Diffusion weighted imaging
- MRA
- Catheter angiography

Or: Perform a follow-up scan at (please circle)
- 1 month
- 6 months
- 1 year
- >1 year

with (please tick all that apply)
- T1 and T2 weighted imaging
- Proton density weighted imaging
- Fluid-attenuated inversion recovery imaging
- T1 weighted imaging + contrast
- Gradient echo imaging
- Diffusion weighted imaging
- MRA
- Catheter angiography

D If there is another cavernoma-like lesion, go to page 4
If not, go back to page 1 and complete Question 3
The nature, frequency and natural history of intracranial cavernous malformations in adults
Appendix 14

See attached paper that follows.