Genetic Alliance UK
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Cavernoma Alliance UK
Helping the Cavernoma Community

Guidelines for the management of cerebral cavernous malformations in adults

Genetic Alliance UK

Genetic Alliance UK is the national charity of 154 patient organisations supporting all those affected by genetic conditions. We aim to improve the lives of people affected by rare genetic conditions by ensuring high quality services and information are available to all who need them. We provide a united voice for all those affected by rare genetic conditions, enabling us to work together towards a common goal of making life better for patients, their families and carers.

Genetic Alliance UK undertakes various projects and programmes that adds evidence and knowledge to improve health service provision, research and support for families. These initiatives include:

- The Facilitating Networks project. This project sought to address the difficulties that children, adults and families with rare genetic disorders experience in receiving good information and optimal healthcare for their condition. The primary aim of the project was to work with small Patient Support groups to facilitate the development of networks of health and social care professionals in order to improve information, care and services for patients and families affected by, or at risk of, rare genetic disorders.
- Rare Disease UK, a multi-stakeholder group working together to inform and influence health departments and the NHS to develop a plan for rare diseases, which includes the information and support they require under the management of their care.
- Route Maps for Rare Conditions, a project involving ten of our small member groups developing a practical and cost-effective framework for improving information, access and coordination of health and social care services for individuals and families with a wide range of rare genetic conditions.

Cavernoma Alliance UK

Cavernoma Alliance UK (CA UK), formed in February 2005 and constituted as a registered charity in July of the following year, is comprised of cavernoma patients from all over the UK along with a board of trustees.

The charity's mission is to improve the quality of life for those affected by either single or multiple cavernomas through information, education and promotion of research. CA UK aims to provide a support group for those with cavernoma through events such as an international forum in London, regional meetings, CaverClinics, groups for young persons and their families and a mailing list. CA UK also aims to make the general public aware of this common condition.

Members include individuals diagnosed with either single or multiple cavernomas, those waiting for diagnosis, and family, friends or carers. Membership is free and helps CA UK establish the condition as a recognised neurological disorder.

CA UK has well-established links with healthcare professionals and services, nationally and internationally. This means CA UK keeps abreast of new information and research for the Cavernoma community.

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Guidelines for the management of cerebral cavernous malformations in adults

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These guidelines can be downloaded from:

www.geneticalliance.org.uk/docs/managementofccm.pdf

www.cavernoma.org.uk

Table of contents

1. Introduction

1.1 A cerebral cavernous malformation (CCM) is a collection of abnormal blood vessels, within which blood flows slowly. Blood is prone to ooze through the leaky junctions between the cells that make up the walls of CCMs. CCMs are also known as 'cavernomas', 'cavernous angiomas', or 'cavernous haemangiomas'. Most CCM occur sporadically (in other words, for no apparent reason), but they may also be inherited as an autosomal dominant trait.

1.2 CCMs are common in the general population. If people who do not have neurological symptoms undergo brain magnetic resonance imaging (MRI), one in approximately 600 will be found to have a CCM [Morris et al. 2009]. However, only a small proportion of these people come to medical attention because most people without neurological symptoms do not undergo brain MRI. Annual CCM detection rates were approximately one per 500,000 in the USA in 1965-1992 and three per 500,000 in Scotland in 1999-2000, which may be explained by the increasing availability and use of brain MRI [Brown, Jr. et al. 1996; Al-Shahi et al. 2003].

1.3 CCM can cause a variety of neurological symptoms. When neurological symptoms lead to a CCM diagnosis in adults, one quarter are due to intracranial haemorrhage, another quarter are due to a focal neurological deficit without radiographic evidence of recent haemorrhage [Al-Shahi Salman et al. 2008], and the remainder present with epileptic seizures [Al-Shahi et al. 2003; Josephson et al. 2011]. Because CCM are common and can be found incidentally, careful consideration is required to determine whether a CCM has caused symptoms or not.

1.4 Expert interpretation of brain imaging is required to diagnose CCM and to determine whether a CCM has bled. CCM have a recognisable appearance on MRI (figure 1). However, if someone comes to medical attention with an intracerebral haemorrhage (ICH), it can take at least two or three months for the blood products on brain imaging to recede and an underlying CCM to be seen on brain MRI [Al-Shahi Salman et al. 2008]. Furthermore, if someone has a new "focal neurological deficit" (FND) – such as weakness or numbness – attributable to the anatomical location of a CCM, brain imaging of the right type needs to be performed at the right time in relation to the start of the symptoms to detect whether the symptoms were due to ICH or not [Al-Shahi Salman et al. 2008].

1.5 The risk of symptomatic haemorrhage from CCM varies between people. The annual risk of a first-ever ICH is 0.4%-0.6% (figure 2). After a first ICH, the annual risk of a second ICH is higher and lies somewhere between 3.8% to 22.9% (figure 2). However, the risk of a second ICH decreases over time [Al-Shahi Salman et al. 2012; Flemming et al. 2012; Barker II et al. 2001; Wang et al. 2003]. Studies have not been consistent about whether female sex or brainstem CCM location raise the risk of ICH. The risk of dying within one month after CCM ICH appears low [Al-Shahi Salman et al. 2012], but appears to be higher after second ICHs from brainstem CCM [Fritschi et al. 1994].

1.6 Despite existing knowledge about CCM, doctors and their patients frequently encounter diagnostic and therapeutic questions about CCM. Therefore, we sought to address these questions with guidelines based on diagnostic test accuracy studies and controlled studies of CCM treatment in adults.

2. Methods of developing this guideline

2.1 We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group's recommendations for developing these guidelines, involving two separate processes of grading the quality of the evidence available and then grading the strength of each recommendation in the guidelines (www.gradeworkinggroup.org) [Atkins et al. 2004].

Identification of questions

2.2 We formulated our specific management questions by consensus, using the PICO principle by specifying for each question: Patients [i.e. adults with CCM], Intervention/Indicator, Comparator/Control, and the Outcome of interest. We identified important outcomes in discussion with the two patient support groups involved with the creation of these guidelines. We judged the relative importance of the outcomes, and prioritised death and new or worsened clinically symptomatic FNDs (whether or not new ICH had been confirmed by imaging or pathological examination).

Literature search

2.3 We used electronic strategies (Appendix 1) to search for journal articles about CCM published prior to 1 January 2011 and indexed in OVID Medline and Embase. Pairs of the group of three reviewers (NS, MP and RA-SS) reviewed the titles and abstracts of eligible articles and excluded articles if: they were reviews and did not report original data, they did not address our specific management questions, they were exclusive to children with CCM, they reported fewer than 20 adults with CCM, we were unable to extract relevant data from the article, or they were not designed to address our specific PICO questions (Appendix 2). If there were disagreements or uncertainties amongst the pair of reviewers, they were arbitrated by a third reviewer.

Grading the quality of the evidence

2.4 Pairs of the group of three reviewers (NS, MP and RA-SS) independently graded the quality of evidence available in each of the remaining articles pertinent to diagnostic and therapeutic questions using the Centre for Evidence-Based Medicine (CEBM) Levels of Evidence published in 2011 (http://www.cebm.net/index.aspx?o=5653). For studies of diagnostic test accuracy, we sought studies graded as Level 1 (systematic review of cross sectional studies with a consistently applied reference standard and blinding) or Level 2 (individual cross sectional studies with consistently applied reference standard and blinding). For studies of the benefits and harms of treatments, we sought studies graded as Level 1 (systematic review of randomised trials or n-of-1 trials) or Level 2 (randomised trial or observational study with dramatic effect). We used a published definition of a dramatic effect in an observational treatment study, "a sufficiently extreme difference between the outcome ranges for treated and untreated patients might be defined by two rules: (a) that the conventionally calculated probability of the two groups of observations coming from the same population should be less than 0.01 and (b) that the estimate of the treatment effect (rate ratio) should be large… We suggest that rate ratios beyond 10 are highly likely to reflect real treatment effects, even if confounding factors associated with the treatment may have contributed to the size of the observed associations." [Glasziou et al. 2007]. If there appeared to be a dramatic effect in an observational treatment study we also judged whether the risk of bias in the study was high, and if it was the article was excluded (Appendix 2). Three reviewers (NS, MP and RA-SS) agreed on the overall quality of the evidence relevant to each PICO question which was available after this selection process, and other members of the guidelines panel approved the final grading.

2.5 Two reviewers (CR and JB) independently reviewed a selection of the articles that RA-SS identified as being potentially relevant to the genetic questions in these guidelines from the literature search (Appendix 1). In the absence of CEBM criteria for grading the quality of the evidence in genetic testing studies, CR and JB identified articles that they thought best answered these questions.

Grading the strength of recommendations

2.6 After considering the grade of the quality of the evidence available for each PICO question described in a document circulated electronically, the guidelines panel incorporated their judgments about the underlying values and preferences related to the management options and outcomes, the balance of desirable and undesirable effects, and the balance of net benefits and cost, culminating in a recommendation [Atkins et al. 2004]. In a consensus discussion, the guidelines panel felt unable to grade the strength of their recommendations in the light of the quality of the evidence available.

3. Diagnostic guidelines

3.1 Prior to the use of brain MRI in clinical practice in the 1980s, CCM were often classified as angiographically-occult (or 'cryptic') vascular malformations if histological examination had not been undertaken to definitively diagnose CCM [Tomlinson et al. 1994]. The typical appearance of CCM on T1- and T2-weighted MRI sequences was described in an un-blinded study of ten patients with pathologically-confirmed CCM in 1987 [Rigamonti et al. 1987]. A wider variety of MRI appearances has been described subsequently [Schefer et al. 1991; Zabramski et al. 1994].

3.2 We have limited these diagnostic guidelines to studies testing the accuracy of CCM diagnostic criteria applied to a consecutive series using a pathological reference standard and MRI as the index test.

3.3 Our criteria were met by one study of 72 patients with brain masses accompanied by vasogenic oedema and substantial amounts of blood, which found that a T1 hyperintense perilesional signal could differentiate CCM from other causes with excellent specificity (98%) and reasonable sensitivity (62%) [Yun et al. 2008].

3.4 We excluded potentially eligible studies because: they were restricted to patients meeting CCM MRI diagnostic criteria thus precluding identification of false negatives [Frischer et al. 2008], they were restricted to lesions consistent with CCM on histological examination thus precluding identification of false positives [Schefer et al. 1991; Tomlinson et al. 1994], observers were not blinded to the index test or reference standard [Tomlinson et al. 1994; Pinker et al. 2006; Biondi et al. 1986; Biondi and Scialfa 1988]), or we were unable to extract relevant data [Biondi et al. 1986; Biondi and Scialfa 1988].

3.5 MRI sequences sensitive to the magnetic susceptibility artefact of iron (such as gradient echo and susceptibility-weighting) have been found to be more sensitive for the detection of multiple CCM in comparison to conventional spin echo in studies undertaken in families with inherited CCM (but without pathological confirmation) [Campbell et al. 2010].

3.6 The detection of recent haemorrhage from a CCM is dependent on the use of the appropriate imaging modality at the appropriate time to detect acute or subacute blood products. This is relevant to both clinical practice and research, which has led to definitions and reporting standards for diagnosing CCM haemorrhage [Al-Shahi Salman et al. 2008], although these criteria have not been validated.

3.7 We recommend that brain MRI using T1-weighted, T2-weighted, and haem-sensitive sequences should be performed to: (a) investigate patients with brain masses accompanied by vasogenic oedema and substantial amounts of blood, (b) diagnose CCM and (c) determine whether CCM are solitary or multiple. Reference should be made to CCM diagnostic criteria and definitions and reporting standards for CCM haemorrhage [Rigamonti et al. 1987; Al-Shahi Salman et al. 2008].

4. Therapeutic guidelines

4.1 We have limited these therapeutic guidelines to studies of CCM treatment involving at least 20 adults, that examined surgical resection [Bertalanffy et al. 2002] and/or stereotactic radiosurgery [Steiner et al. 2010], in which a group of adults receiving treatment was compared to either another group receiving a different treatment or to a conservatively-managed (untreated) group of adults. We have stratified our specific management questions by adults' mode of clinical presentation because the future risks of haemorrhage from CCM appear may be higher if the CCM initially comes to medical attention with a haemorrhage (see section 1.5 and Figure 2). We sought to further stratify the answers to specific management questions by CCM location (because it too may influence the future risk of haemorrhage, Figure 2), and to distinguish outcomes for adults with solitary or multiple CCM.

How should an adult with an incidentally-discovered CCM be managed?

4.2 Our criteria were not met by any studies of adults with incidentally-discovered CCM, comparing two different management strategies for reducing the risk of future ICH or FND, or improving functional outcome.

4.3 We recommend that decisions about the treatment of adults with incidentally-discovered CCM be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults.

How should an adult with a CCM that has caused one ICH or FND be managed?

4.4 Our criteria were not met by any studies of adults with CCM that had already caused one ICH or FND, comparing two different management strategies for reducing the risk of future ICH or FND, or improving functional outcome.

4.5 We excluded five potentially eligible observational studies [Yoon et al. 1998; Tarnaris et al. 2008; Esposito et al. 2003; Huang et al. 2010; Mathiesen et al. 2003] because none of them demonstrated dramatic effects. Three studies compared surgery with conservative management in a total of 81 adults with brainstem CCM [Esposito et al. 2003; Tarnaris et al. 2008; Huang et al. 2010]; one study compared Gamma Knife stereotactic radiosurgery with conservative management in 41 adults with CCM in any location [Yoon et al. 1998]; and one study compared surgery with Gamma Knife stereotactic radiosurgery with conservative management in 68 adults with deep and brainstem CCM [Mathiesen et al. 2003].

4.6 We recommend that decisions about the treatment of adults with CCM that have already caused one ICH or FND be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults.

How should an adult with a CCM that has caused more than one ICH or FND be managed?

4.7 Our criteria were not met by any studies of adults with CCM that had caused more than one ICH or FND, comparing two different management strategies for reducing the risk of future ICH or FND, or improving functional outcome.

4.8 We recommend that decisions about the treatment of adults with CCM that have caused more than one ICH or FND be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults.

How should an adult with a CCM that has caused epileptic seizure(s) be managed?

4.9 The risk of developing epilepsy for adults with a CCM during the five years after a first seizure is high (94%) [Josephson et al. 2011]. The chance of becoming free of seizures for two years for adults with a CCM during the five years after a diagnosis of epilepsy is moderate (47%) [Josephson et al. 2011], and CCM are known to cause intractable epilepsy [von der Brelie and Schramm 2011].

4.10 Our criteria were not met by any studies of adults with CCM that had caused a first seizure or epilepsy, comparing two different management strategies for reducing the risk of future seizures or improving functional outcome. Our findings were corroborated by one systematic review of studies of surgery for adults with CCM and intractable epilepsy, which found several methodological problems with the current literature [von der Brelie and Schramm 2011].

4.11 We excluded eleven potentially eligible observational studies [Secchi et al. 1998; Rougier et al. 1989; Congia et al. 2001; Noto et al. 2005; Shih and Pan 2005; Banfi et al. 2006; Hsu et al. 2007; Vespignani et al. 1994; Iakovlev et al. 2005; Kivelev et al. 2009; Yeon et al. 2009]. Two studies appeared to show a dramatic effect, but we excluded both of them because we judged them to be at high risk of bias: one compared 14 adults with CCM undergoing surgical resection with 16 adults with CCM undergoing Gamma Knife stereotactic radiosurgery [Shih and Pan 2005] and the other study compared 16 adults with CCM undergoing surgical resection to 15 adults who were managed conservatively [Noto et al. 2005]. Nine further studies did not demonstrate dramatic effects: seven compared surgery with conservative management in 204 adults with supratentorial CCMs [Rougier et al. 1989; Secchi et al. 1998; Congia et al. 2001; Banfi et al. 2006; Vespignani et al. 1994; Kivelev et al. 2009; Iakovlev et al. 2005], one study compared surgery with radiosurgery in 29 adults with CCMs in any supratentorial location [Hsu et al. 2007], and one study compared lesionectomy with other types of surgical resection in 56 adults with CCMs in any supratentorial location [Yeon et al. 2009].

4.12 We recommend adherence to existing guidelines for the management of first seizures and epilepsy in general [Scottish Intercollegiate Guidelines Network 2005; National Institute for Health and Clinical Excellence 2012], given the absence of randomised trials or observational studies with dramatic effects for adults with a CCM that has caused a first seizure or epilepsy.

How should CCM be managed in mothers before, during, and after birth?

4.13 Our criteria were not met by any studies of mothers with CCM, comparing two different management strategies before, during or after birth for reducing the risk of future ICH or FND, or improving functional outcome.

4.14 We excluded a few case reports of different outcomes for mothers with CCM during pregnancy, and one observational cohort study of 85 women that did not find any ICH or FND during pregnancy [Porter et al. 1997]. We found one narrative review article stating that caesarean section may be indicated and pregnancy may be contraindicated for some women with CCM [Labauge et al. 2007], but we could not support this finding in the light of current evidence.

4.15 We recommend that decisions about the treatment of mothers with CCM be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these women.

Should the existence of a CCM influence the prescription of antithrombotic or thrombolytic medications?

4.16 Our criteria were not met by any studies comparing two different antithrombotic or thrombolytic management strategies for adults with vaso-occlusive disease who also had a CCM.

4.17 We excluded a few case reports of different outcomes for adults with CCM who received antithrombotic or thrombolytic therapy [Califf 1999; Henninger et al. 2010; Pozzati et al. 2006; The Stroke Prevention in Atrial Fibrillation Investigators 1996]. We found one narrative review article that recommended that anticoagulant treatment should be contraindicated for adults with CCM [Labauge et al. 2007], but we could not support this finding in the light of current evidence.

4.18 We recommend that decisions about antithrombotic or thrombolytic treatment of adults with CCM be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults. We recommend that clinicians bear in mind the beneficial effects of antithrombotic and thrombolytic drugs shown for some vaso-occlusive diseases in randomised controlled trials, which will have included some adults with CCM.

5. Genetic guidelines

What is the likelihood of finding a mutation in the CCM1, CCM2 or CCM3 genes?

5.1 Part of the assessment of the likelihood of finding a mutation involves knowing whether an adult has a family history of ICH, FND, or epilepsy (which requires careful questioning), whether any relatives have a CCM on MRI, and whether or not the proband has multiple CCM (requiring haem-sensitive MRI sequences – see section 3.5).

5.2 JB was not aware of any criteria available to grade the quality of evidence evaluating decisions to test adults with CCM for a genetic mutation, and considered the CEBM criteria for grading the quality of evidence in diagnostic test accuracy studies to be inapplicable for the purposes of these guidelines, as the effective gold standard for a genetic diagnosis is a combination of phenotypic assessment with genotype information. Therefore, CR and JB sought studies of the frequency of genetic mutations or deletions in the CCM 1, 2, and 3 genes in three groups of adults with CCM: (1) adult with a single CCM but no family history, (2) adult with at least one CCM and a family history, and (3) adult with multiple CCMs but no family history. Papers included had completed analysis of at least one entire gene by a PCR-mutation detection strategy, with or without deletion analysis by multiplex ligation-dependent probe amplification (MLPA). Papers with a risk of bias by inclusion of a significant Hispanic cohort were excluded.

5.3 CR and JB included five studies [D'Angelo et al. 2011; Denier et al. 2006; Reich et al. 2003; Verlaan et al. 2004b; Verlaan et al. 2004a]. In studies investigating adults with single CCM but no family history, it was unclear whether every person had undergone haem-sensitive brain MRI, but despite this mutation detection rates were very low. The frequency of the detection of mutations or deletions was:

- adult with a single CCM but no family history: 0% to 1%
- adult with at least one CCM and a family history: 78% to 94%
- adult with multiple CCMs but no family history: 57%

5.4 We do not recommend mutation analysis in the CCM 1, 2, and 3 genes for adults without a family history and only one CCM on haem-sensitive brain MRI sequences. We recommend that mutation analysis be considered by adults with CCM(s) and a family history of CCM, and by adults with multiple CCM and no family history.

6. Other guidelines

Which professional groups should manage adults with CCMs?

6.1 We were unable to find guidelines on which professional groups should manage adults with CCMs. However, we recommend that any adult with a CCM should be seen by a neurologist or neurosurgeon with a vascular sub-specialty interest who can advise on the treatment of CCMs. Any adult with a CCM causing one or more epileptic seizures should be seen by an appropriate specialist, in keeping with epilepsy management guidelines [Scottish Intercollegiate Guidelines Network 2005; National Institute for Health and Clinical Excellence 2012]. Adults concerned about pre-symptomatic genetic testing should see a clinical geneticist prior to any testing being undertaken.

What information is available for patients?

6.2 Information suitable for patients with CCM can be found on the websites of the UK support organisation Cavernoma Alliance UK (www.cavernoma.org.uk), NHS Choices (www.nhs.uk/conditions/cavernoma/Pages/Introduction.aspx) or the USA support organisation Angioma Alliance (www.angiomaalliance.org). Advice for patients concerned about genetic testing is available from Genetic Alliance UK (www.geneticalliance.org.uk).

7. Recommendations for future research

7.1 These guidelines have identified major deficiencies in the quality of the evidence that is available to inform the management of adults with CCM.

7.2 In particular, given the absence of randomised controlled trials and the large number of observational studies of CCM treatment (a) without a comparison group, or (b) not showing a dramatic effect in an observational study, or (c) at high risk of bias, randomised controlled trials are required.

7.3 Well-designed studies of the diagnostic accuracy of brain MRI for identifying CCM are also required.

7.4 Future studies of the frequency of genetic mutations, and the clinical outcomes for carriers, should carefully phenotype family histories according to their type and the symptomatic status of affected relatives, as well as the MRI sequences used to establish CCM multiplicity.

8. Summary

8.1 We found few published studies of the diagnosis and treatment of CCMs of level 1 or 2 quality according to the Centre for Evidence-Based Medicine's 2011 criteria (http://www.cebm.net/index.aspx?o=5653), which enabled us to make few specific recommendations for the clinical investigation and management of adults with CCMs.

8.2 We recommend that diagnostic imaging with brain MRI using T1-weighted, T2-weighted, and haem-sensitive sequences should be performed to: (a) investigate patients with brain masses accompanied by vasogenic oedema and substantial amounts of blood, (b) diagnose CCM and (c) determine whether CCM are solitary or multiple. Reference should be made to CCM diagnostic criteria and definitions and reporting standards for CCM haemorrhage [Rigamonti et al. 1987; Al-Shahi Salman et al. 2008].

8.3 We recommend that decisions about the treatment of adults with incidentally-discovered CCM be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults.

8.4 We recommend that decisions about the treatment of adults with CCM that have already caused one ICH or FND be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults.

8.5 We recommend that decisions about the treatment of adults with CCM that have caused more than one ICH or FND be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults.

8.6 We recommend adherence to existing guidelines for the management of first seizures and epilepsy in general, given the absence of randomised trials or observational studies with dramatic effects for adults with a CCM that has caused a first seizure or epilepsy.

8.7 We recommend that decisions about the treatment of mothers with CCM be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these women.

8.8 We recommend that decisions about antithrombotic or thrombolytic treatment of adults with CCM be made on a case-by-case basis, given the absence of randomised trials or observational studies with dramatic effects specific to these adults. We recommend that clinicians bear in mind the beneficial effects of antithrombotic and thrombolytic drugs shown for some vaso-occlusive diseases in randomised controlled trials, which will have included some adults with CCM.

8.9 We do not recommend mutation analysis in the CCM 1, 2, and 3 genes for adults without a family history and only one CCM on haem-sensitive brain MRI sequences. We recommend that mutation analysis be considered by adults with CCM(s) and a family history of CCM, and by adults with multiple CCM and no family history.

9. Conflicts of interest

RA-SS has received funding for research from the Medical Research Council, the Stroke Association, Chest Heart and Stroke Scotland, the Chief Scientist Office of the Scottish Government Health Department, and Cavernoma Alliance UK. NS has received funding from the Medical Research Council and the Stroke Association. MP, KK, IS, CR, JB, and NK have not declared any competing interests.

10. Acknowledgements

The creation of these guidelines was jointly funded by Cavernoma Alliance UK and a Facilitating Networks grant to Genetic Alliance UK. NS was funded by a Medical Research Council / Stroke Association clinical research training fellowship. RA-SS was funded by a Medical Research Council senior clinical fellowship.

Figure 1: cerebral cavernous malformation on brain magnetic resonance imaging

Cross-sectional T2-weighted magnetic resonance image, demonstrating a solitary cerebral cavernous malformation (arrows) in the temporal lobe of the brain.

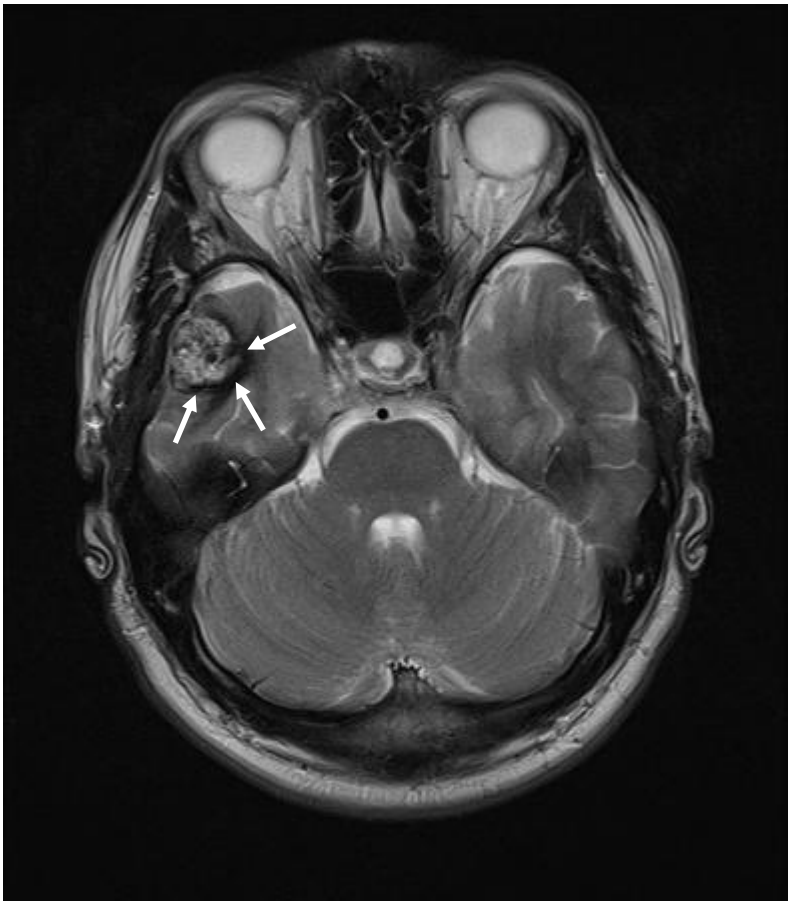
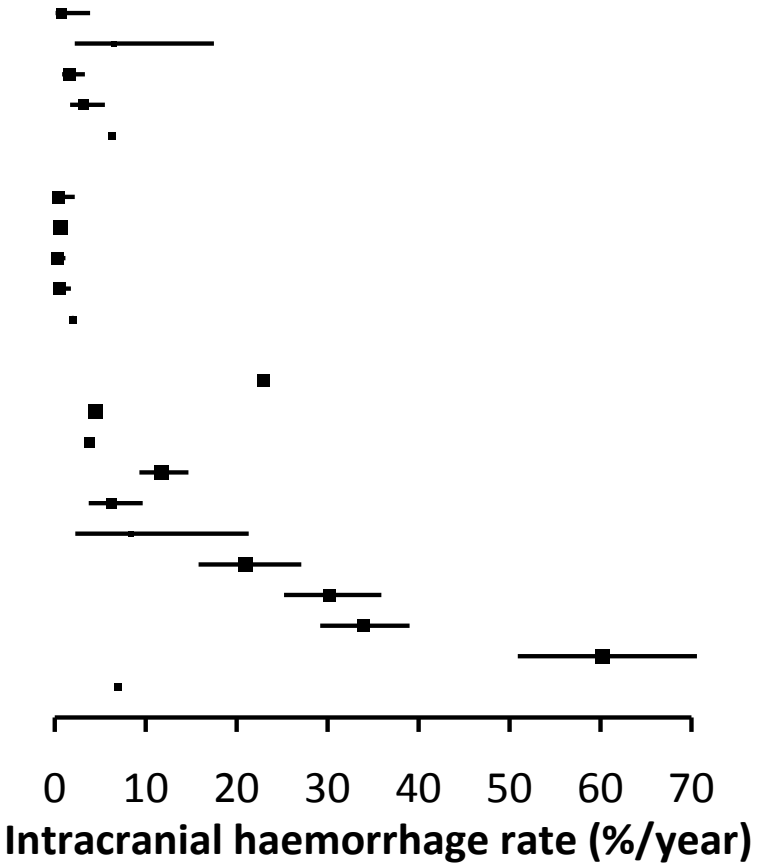


Figure 2: risk of symptomatic intracranial haemorrhage during follow-up in studies of the untreated clinical course of >20 participants with cerebral cavernous malformations.

Areas of point estimates are proportional to the sample size of each study. Error bars represent 95% confidence intervals (if available or calculable).

Study	Selection criteria	Sample size	Mean follow-up (yrs)
First/recurrent intracranial haemorrhage not distinguished			
Robinson *et al.* 1991	None	66	2·2
Zabramski *et al.* 1994	Familial	21	2·2
Porter *et al.* 1997	None	110	3·8
Moriarity *et al.* 1999	None	68	5·2
Ghannane *et al.* 2007	None	39	2·5
First intracranial haemorrhage			
Aiba *et al.* 1995	None	110	4·7
Kondziolka *et al.* 1995	None	122	2·8
Flemming *et al.* 2012	None	108	7·3
Al-Shahi Salman *et al.* 2012	None	96	5·0
Mathiesen *et al.* 2003	Brainstem and deep	34	4·6
Recurrent intracranial haemorrhage			
Aiba *et al.* 1995	None	110	4·7
Kondziolka *et al.* 1995	None	122	2·8
Kim *et al.* 1997	None	62	1·9
Barker *et al.* 2001	None	136	3·8
Flemming *et al.* 2012	None	74	7·3
Al-Shahi Salman *et al.* 2012	None	18	5·0
Fritschi *et al.* 1994	Brainstem	139	2·5
Porter *et al.* 1999	Brainstem	100	2·0
Hasegawa *et al.* 2002	Brainstem	83	4·3
Wang *et al.* 2003	Brainstem	137	1·8
Mathiesen *et al.* 2003	Brainstem and deep	34	4·6



Appendix 1: electronic search strategies

Medline

1. Hemangioma, Cavernous, Central Nervous System/
2. Hemangioma, Cavernous/
3. (cavernous adj5 (angioma$ or hemangioma$ or malformation$)).tw.
4. cavernoma$.tw.
5. 2 or 3 or 4
6. exp brain/ or central nervous system/ or exp cerebral arteries/
7. exp brain neoplasms/
8. (brain$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw.
9. 6 or 7 or 8
10. 10. 5 and 9
11. 11. 1 or 10

Embase

1. Brain Hemangioma/
2. brain ventricle cavernoma/
3. cavernous hemangioma/
4. (cavernous adj5 (angioma$ or hemangioma$ or malformation$)).tw.
5. cavernoma$.tw.
6. 3 or 4 or 5
7. central nervous system/ or exp brain/ or exp brain ventricle/ or exp brain artery/
8. exp brain tumor/
9. (brain$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw.
10. 10. 7 or 8 or 9
11. 11. 6 and 10
12. 12. 1 or 2 or 11

Appendix 2: excluded studies, with the reasons for their exclusion

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[American Society of Interventional and Therapeutic Neuroradiology 2000]			*					
[Abla *et al.* 2010a]				*				
[Abla *et al.* 2010b]			*					
[Acciarri *et al.* 1993]						*		
[Acciarri *et al.* 1995]						*		
[Aiba *et al.* 1995]					*			
[Akdemir, I 2009]						*		
[Al-Shahi Salman *et al.* 2008]		*						
[Alemany *et al.* 2004]		*						
[Amin-Hanjani *et al.* 1998a]						*		
[Amin-Hanjani *et al.* 1998b]						*		
[Amin-Hanjani and Ogilvy 1999]			*					
[Asaad *et al.* 2010]			*					
[Attar *et al.* 2001]						*		
[Awad and Jabbour 2006]			*					
[Azam and O'Donovan 2009]				*				
[Banfi *et al.* 2006]							*	
[Barker II *et al.* 1997]		*						
[Barker II *et al.* 2001]		*						
[Barnes *et al.* 2000]			*					

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Bartolomei *et al.* 1999]						*		
[Baumann *et al.* 2006]		*						
[Baumann *et al.* 2007]						*		
[Belousova *et al.* 2003]					*			
[Berg *et al.* 2000]				*				
[Bernotas *et al.* 2009]						*		
[Bertalanffy *et al.* 1991]						*		
[Bertalanffy *et al.* 1992]						*		
[Bertalanffy *et al.* 2002]						*		
[Bhardwaj *et al.* 2009]				*				
[Biondi *et al.* 1986]						*		
[Biondi and Scialfa 1988]					*			
[Blamek *et al.* 2010]						*		
[Bradley Jr. 1993]		*						
[Braun *et al.* 1996]						*		
[Bruneau *et al.* 2006]						*		
[Brunon and Nuti 2007]			*					
[Califf 1999]			*					
[Cantu *et al.* 2005]		*						
[Cappabianca *et al.* 1997]						*		
[Casazza *et al.* 1996]						*		
[Chang *et al.* 2009]						*		

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Chang *et al.* 2001]		*						
[Chang *et al.* 1998]						*		
[Chaskis and Brotchi 1998]			*					
[Chazal *et al.* 2007]			*					
[Chen *et al.* 1997]						*		
[Chul *et al.* 2001]				*				
[Cohen *et al.* 1995]						*		
[Cohen-Gadol *et al.* 2006]						*		
[Congia *et al.* 2001]							*	
[Consales *et al.* 2010]				*				
[Cordonnier *et al.* 2008]		*						
[Cosgrove 1999]			*					
[Cristofori *et al.* 1998]						*		
[D'Angelo *et al.* 2006]						*		
[de Oliveira *et al.* 2010]						*		
[De Santis *et al.* 2003]						*		
[Deshmukh *et al.* 2002]			*					
[Deshmukh 2004]			*					
[Di Rocco *et al.* 1996]				*				
[Di Rocco *et al.* 1997a]				*				
[Di Rocco *et al.* 1997b]				*				
[Dodick *et al.* 1994]						*		

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Duckworth 2010]			*					
[Enchev *et al.* 2008]						*		
[Engel Jr. 2006]			*					
[Esposito *et al.* 2003]							*	
[Fahlbusch and Strauss 1991]							*	
[Faria *et al.* 2004]						*		
[Farmer *et al.* 1988]						*		
[Ferroli *et al.* 2005]						*		
[Ferroli *et al.* 2006]						*		
[Flickinger *et al.* 1998]			*					
[Frim *et al.* 1996]		*						
[Frischer *et al.* 2008]						*		
[Gamrot *et al.* 2005]						*		
[Garrett and Spetzler 2009]			*					
[Ghannane *et al.* 2007]					*			
[Giliberto *et al.* 2010]			*					
[Goel *et al.* 2001]			*					
[Gralla *et al.* 2003]						*		
[Gross *et al.* 2009b]			*					
[Gross *et al.* 2009a]			*					
[Grunert *et al.* 2003]		*						
[Hahn *et al.* 1991]					*			

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Hammen *et al.* 2007]		*						
[Hardy *et al.* 1990]		*						
[Hasegawa *et al.* 2002]						*		
[Hauck *et al.* 2009]						*		
[Houtteville 1995]			*					
[Houtteville 1997]						*		
[Hsu *et al.* 2007]							*	
[Huang *et al.* 2010]							*	
[Huang *et al.* 2006]						*		
[Huo *et al.* 2008]						*		
[Iakovlev *et al.* 2005]							*	
[Jackowski *et al.* 1992]						*		
[Jovanovic *et al.* 2005]						*		
[Jovanovic *et al.* 2008a]					*			
[Jovanovic *et al.* 2008b]						*		
[Kameyama and Kakita 2007]	*							
[Kang *et al.* 2001]		*						
[Karlsson *et al.* 1998]						*		
[Kayali *et al.* 2004]					*			
[Khalil *et al.* 2007]			*					
[Khouri *et al.* 2007]			*					
[Kida *et al.* 1995a]						*		

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Kida *et al.* 1995b]						*		
[Kida *et al.* 1999]			*					
[Kida and Kida 2009]						*		
[Kidwell and Wintermark 2008]			*					
[Kim *et al.* 2002]		*						
[Kim *et al.* 2005]						*		
[Kivelev *et al.* 2009]							*	
[Kloet *et al.* 1996]			*					
[Kobayashi *et al.* 2007]		*						
[Komotar *et al.* 2008]			*					
[Kondziolka *et al.* 1990]						*		
[Kondziolka *et al.* 1995]						*		
[Kondziolka *et al.* 2007]						*		
[Kraemer and Awad 1994]			*					
[Kuncz *et al.* 1994]			*					
[Lapras *et al.* 1989]						*		
[Lapras *et al.* 1990]				*				
[Lerch *et al.* 1994]						*		
[Lewis *et al.* 1995]					*			
[Li *et al.* 2009]						*		
[Li 2007]						*		
[Liscak *et al.* 2000]						*		

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Liscak *et al.* 2005]						*		
[Liu *et al.* 2005]						*		
[Lonjon *et al.* 1993]						*		
[Luccarelli *et al.* 1981]						*		
[Lunardi and Acqui 1993]						*		
[Lunsford *et al.* 2010]						*		
[Maesawa *et al.* 1999]			*					
[Mahla *et al.* 1999]						*		
[Mao *et al.* 2002]						*		
[Mathiesen *et al.* 2003]							*	
[Mehdorn *et al.* 1998]						*		
[Menzler *et al.* 2010]		*						
[Miyazawa *et al.* 2003]			*					
[Monaco *et al.* 2010]						*		
[Moran *et al.* 1999]					*			
[Nagy *et al.* 2010]						*		
[Nataf *et al.* 2007]						*		
[Noto *et al.* 2005]								*
[Ohue *et al.* 2010]						*		
[Ojemann and Ogilvy 1999]			*					
[Pinker *et al.* 2006]								*
[Pfisterer *et al.* 2002]						*		

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Porter *et al.* 1997]		*						
[Porter *et al.* 2002]			*					
[Porter *et al.* 1999]						*		
[Porter *et al.* 2000]			*					
[Regis *et al.* 2000]						*		
[Rohde *et al.* 2007]						*		
[Rougier *et al.* 1989]							*	
[Rowe 2006]						*		
[Ryvlin *et al.* 1995]		*						
[Samii *et al.* 2001]						*		
[Savoiardo *et al.* 1983]		*						
[Schefer *et al.* 1991]						*		
[Scheuerle *et al.* 2004]						*		
[Secchi *et al.* 1998]							*	
[Shalek *et al.* 2008]						*		
[Sheehan and Schlesinger 2010]			*					
[Shih and Pan 2005]								*
[Smith *et al.* 2002]						*		
[St George *et al.* 2002]			*					
[Stavrou *et al.* 2008]						*		
[Stefan *et al.* 2004]						*		
[Stefan and Hammen 2004]			*					

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Steiner *et al.* 2010]			*					
[Tarnaris *et al.* 2008]							*	
[Tasic *et al.* 2008]			*					
[The Stroke Prevention in Atrial Fibrillation Investigators 1996]		*						
[Tomlinson *et al.* 1994]						*		
[Tsien *et al.* 2001]						*		
[Tu *et al.* 2009]			*					
[Van Gompel *et al.* 2009]		*						
[Van Gompel *et al.* 2010]						*		
[Vaquero *et al.* 1987]						*		
[Vespignani *et al.* 1989]	*							
[Vespignani *et al.* 1994]							*	
[Vinas *et al.* 2002]			*					
[von Essen *et al.* 1996]		*						
[Wang *et al.* 2003]						*		
[Wang *et al.* 2010]						*		
[Wang *et al.* 1995]						*		
[Weber *et al.* 1988]	*							
[Winkler *et al.* 2004]						*		
[Winkler *et al.* 2006]		*						
[Woydt *et al.* 1999]						*		
[Woydt *et al.* 2001]						*		

Author(s)	Unable to obtain article	Did not apply to any PICO question	Review article	Exclusively paediatric patients	Unable to extract data	No comparison group	Observational study without dramatic effect	High risk of bias
[Yeon *et al.* 2009]							*	
[Yoon *et al.* 1998]							*	
[Yun *et al.* 2008]		*						
[Zevgaridis *et al.* 1996]						*		
[Zhang *et al.* 2000]						*		
[Zhao *et al.* 2007a]						*		
[Zhao *et al.* 2005]		*						
[Zhao *et al.* 2007b]						*		

References

Abla AA, Lekovic GP, Garrett M et al. Cavernous malformations of the brainstem presenting in childhood: Surgical experience in 40 patients. Neurosurgery 2010a; 67: 1589-1598.

Abla AA, Turner JD, Mitha AP, Spetzler RF. Surgical approaches to brainstem cavernous malformations. [Review]. Neurosurg Focus 2010b; 29: E8.

Acciarri N, Giulioni M, Padovani R, Galassi E, Gaist G. Surgical management of cerebral cavernous angiomas causing epilepsy. J Neurosurg Sci 1995; 39: 13-20.

Acciarri N, Padovani R, Giulioni M, Gaist G, Acciarri R. Intracranial and orbital cavernous angiomas: a review of 74 surgical cases. Br J Neurosurg 1993; 7: 529-539.

Aiba T, Tanaka R, Koike T, Kameyama S, Takeda N, Komata T. Natural history of intracranial cavernous malformations. J Neurosurg 1995; 83: 56-59.

Akdemir H, Öktem IS, Menkü A, Tucer B, Kamaşak K, Tugcu B. Neuronavigation by intraoperative ultrasound: During intracranial cavernoma resection. Neurosurg Q 2009; 19: 185-189.

Al-Shahi Salman R, Berg MJ, Morrison L, Awad IA, Angioma Alliance Scientific Advisory Board. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. Stroke 2008; 39: 3222-3230.

Al-Shahi Salman R, Hall JM, Horne MA et al. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. Lancet Neurol 2012; 11: 217-224.

Al-Shahi R, Bhattacharya JJ, Currie DG et al. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). Stroke 2003; 34: 1163-1169.

Alemany RM, Stenborg A, Sonninen P, Terent A, Raininko R. Detection and appearance of intraparenchymal haematomas of the brain at 1.5 T with spin-echo, FLAIR and GE sequences: poor relationship to the age of the haematoma. Neuroradiology 2004; 46: 435-443.

American Society of Interventional and Therapeutic Neuroradiology Congress of Neurological Surgeons and American Association of Neurological Surgeons. Program requirements for residency/fellowship education in neuroendovascular surgery/interventional neuroradiology: special report on graduate medical education. Neurosurgery 2000; 46: 1486-1493.

Amin-Hanjani S, Ogilvy CS. Overall surgical results of occult vascular malformations. Neurosurg Clin N Am 1999; 10: 475-483.

Amin-Hanjani S, Ogilvy CS, Candia GJ, Lyons S, Chapman PH. Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron. Neurosurgery 1998a; 42: 1229-1236.

Amin-Hanjani S, Ogilvy CS, Ojemann RG, Crowell RM. Risks of surgical management for cavernous malformations of the nervous system. Neurosurgery 1998b; 42: 1220-1227.

Asaad WF, Walcott BP, Nahed BV, Ogilvy CS. Operative management of brainstem cavernous malformations. [Review]. Neurosurg Focus 2010; 29: E10.

Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. Br Med J 2004; 328: 1490-1494.

Attar A, Ugur HC, Savas A, Yuceer N, Egemen N. Surgical treatment of intracranial cavernous angiomas. J Clin Neurosci 2001; 8: 235-239.

Awad I, Jabbour P. Cerebral cavernous malformations and epilepsy. Neurosurg Focus 2006; 21: e7.

Azam M, O'Donovan DJ. Intracranial cavernous hemangioma and seizures in a newborn infant. J Pediatr 2009; 155: 298.

Banfi P, Guaschino E, Delodovici ML, Peron S, Tomei G, Bono G. Cerebral cavernous angiomas and epilepsy: Clinical features and therapy in 20 cases. Bollettino - Lega Italiana Contro L'Epilessia 2006; 133-134: 125-127.

Barker II FG, Amin-Hanjani S, Butler WE, Lyons S, Ogilvy CS, Ojemann RG, Chapman PH. Risk of rebleeding after first haemorrhage from cerebral cavernous malformations: Natural history and response to proton-beam radiosurgery. Neurosurgery 1997; 41: 720.

Barker II FG, Amin-Hanjani S, Butler WE et al. Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. Neurosurgery 2001; 49: 15-24.

Barnes B, Cawley CM, Barrow DL. Intracerebral hemorrhage secondary to vascular lesions. Neurosurg Clin N Am 2000; 13: 289-297.

Bartolomei F, Regis J, Kida Y et al. Gamma Knife radiosurgery for epilepsy associated with cavernous hemangiomas: a retrospective study of 49 cases. Stereotact Funct Neurosurg 1999; 72 Suppl 1: 22-28.

Baumann CR, Acciarri N, Bertalanffy H et al. Seizure outcome after resection of supratentorial cavernous malformations: a study of 168 patients. Epilepsia 2007; 48: 559-563.

Baumann CR, Schuknecht B, Lo RG et al. Seizure outcome after resection of cavernous malformations is better when surrounding hemosiderin-stained brain also is removed. Epilepsia 2006; 47: 563-566.

Belousova OB, Filatov I, Shishkina LV, Sazonova OB. [Supratentorial cavernomas: clinical picture, diagnosis, treatment]. [Russian]. Zh Vopr Neirokhir Im N N Burdenko 2003; 2-6.

Berg AT, Testa FM, Levy SR, Shinnar S. Neuroimaging in children with newly diagnosed epilepsy: A community-based study. Pediatrics 2000; 106: 527-532.

Bernotas G, Rastenyte D, Deltuva V, Matukevicius A, Jaskeviciene V, Tamasauskas A. Cavernous angiomas: an uncontrolled clinical study of 87 surgically treated patients. Medicina (Kaunas, Lithuania) 2009; 45: 21-28.

Bertalanffy H, Benes L, Miyazawa T, Alberti O, Siegel AM, Sure U. Cerebral cavernomas in the adult. Review of the literature and analysis of 72 surgically treated patients. Neurosurg Rev 2002; 25: 1-53.

Bertalanffy H, Gilsbach JM, Eggert HR, Seeger W. Microsurgery of deep-seated cavernous angiomas: report of 26 cases. Acta Neurochir (Wien) 1991; 108: 91-99.

Bertalanffy H, Kuhn G, Scheremet R, Seeger W. Indications for surgery and prognosis in patients with cerebral cavernous angiomas. Neurol Med Chir (Tokyo) 1992; 32: 659-666.

Bhardwaj RD, Auguste KI, Kulkarni AV, Dirks PB, Drake JM, Rutka JT. Management of pediatric brainstem cavernous malformations: experience over 20 years at the hospital for sick children. J Neurosurg 2009; Pediatrics: 458-464.

Biondi A, Scialfa G. Morphological and blood flow MR findings in cerebral vascular malformations. J Neuroradiol 1988; 15: 253-265.

Biondi A, Scotti G, Scialfa G, Landoni L. Magnetic resonance imaging of cerebral cavernous angiomas. Acta Radiol Suppl 1986; 369: 82-85.

Blamek S, Boba M, Larysz D et al. The incidence of imaging abnormalities after stereotactic radiosurgery for cerebral arteriovenous and cavernous malformations. Acta Neurochir Suppl 2010; 106: 187-190.

Bradley Jr. WG. MR appearance of hemorrhage in the brain. Radiology 1993; 189: 15-26.

Braun V, Antoniadis G, Rath S, Richter HP. [Cavernoma. Indications for surgical removal and outcome]. [German]. Nervenarzt 1996; 67: 301-305.

Brown RD, Jr., Wiebers DO, Torner JC, O'Fallon WM. Incidence and prevalence of intracranial vascular malformations in Olmsted County, Minnesota, 1965 to 1992. Neurology 1996; 46: 949-952.

Bruneau M, Bijlenga P, Reverdin A et al. Early surgery for brainstem cavernomas. Acta Neurochir (Wien) 2006; 148: 405-414.

Brunon J, Nuti C. [Results of surgical treatment]. [French]. Neuro-Chirurgie 2007; 53: 256-261.

Califf RM. Glycoprotein IIb/IIIa blockade and thrombolytics: Early lessons from the SPEED and GUSTO IV trials. American Heart Journal 1999; 138: S12-S15.

Campbell PG, Jabbour P, Yadla S, Awad IA. Emerging clinical imaging techniques for cerebral cavernous malformations: a systematic review. [Review]. Neurosurg Focus 2010; 29: E6.

Cantu C, Murillo-Bonilla L, Arauz A, Higuera J, Padilla J, Barinagarrementeria F. Predictive factors for intracerebral hemorrhage in patients with cavernous angiomas. Neurol Res 2005; 27: 314-318.

Cappabianca P, Alfieri A, Maiuri F et al. Supratentorial cavernous malformations and epilepsy: seizure outcome after lesionectomy on a series of 35 patients. Clin Neurol Neurosurg 1997; 99: 179-183.

Casazza M, Broggi G, Franzini A et al. Supratentorial cavernous angiomas and epileptic seizures: preoperative course and postoperative outcome. Neurosurgery 1996; 39: 26-32.

Chang EF, Gabriel RA, Potts MB, Garcia PA, Barbaro NM, Lawton MT. Seizure characteristics and control after microsurgical resection of supratentorial cerebral cavernous malformations. Neurosurgery 2009; 65: 31-37.

Chang HS, Hongo K, Nakagawa H, Tsuge T. Surgical decision-making on cerebral cavernous malformations. J Clin Neurosci 2001; 8: 416-420.

Chang SD, Levy RP, Adler JR, Martin DP, Krakovitz PR, Steinberg GK. Stereotactic radiosurgery of angiographically occult vascular malformations: a 14 year experience. Neurosurgery 1998; 43: 213-220.

Chaskis C, Brotchi J. The surgical management of cerebral cavernous angiomas. Neurol Res 1998; 20: 597-606.

Chazal J, Khalil T, Sakka L. [Therapeutic indications for central nervous system cavernomas.]. [French]. Neuro-Chirurgie 2007; 53: 251-255.

Chen S-J, Tu Y-K, Liu H-M, Lin S-M, Kao M-C, Hung C-C. Cavernoma of the central nervous system: Surgical experience in the magnetic resonance imaging era. Acta Neurologica Taiwanica 1997; 6: 171-178.

Chul SD, Alvarez H, Bhattacharya JJ, Rodesch G, Lasjaunias PL. Intracranial haemorrhage within the first two years of life. Acta Neurochir (Wien) 2001; 143: 997-1004.

Cohen DS, Zubay GP, Goodman RR. Seizure outcome after lesionectomy for cavernous malformations. J Neurosurg 1995; 83: 237-242.

Cohen-Gadol AA, Jacob JT, Edwards DA, Krauss WE. Coexistence of intracranial and spinal cavernous malformations: a study of prevalence and natural history. J Neurosurg 2006; 104: 376-381.

Congia S, Saba S, Cannas A, Mascia MM, Tuveri A, Casula A, Onali E, Pinna F, Mascia G, Mela A. Epileptic seizures and cavernous angiomas. Bollettino - Lega Italiana Contro L'Epilessia 2001; 113-114: 163-166.

Consales A, Piatelli G, Ravegnani M et al. Treatment and outcome of children with cerebral cavernomas: A survey on 32 patients. Neurol Sci 2010; 31: 117-123.

Cordonnier C, Al-Shahi Salman R, Bhattacharya JJ et al. Differences between intracranial vascular malformation types in the characteristics of their presenting haemorrhages: prospective, population-based study. J Neurol Neurosurg Psychiatry 2008; 79: 47-51.

Cosgrove GR. Occult vascular malformations and seizures. Neurosurg Clin N Am 1999; 10: 527-535.

Cristofori L, Gambin R, Tassetti R, Vivenza C, Turazzi S, Bricolo A. Epileptogenic cavernous angiomas: The role of surgery in 63 patients. Riv Neurobiol 1998; 44: 609-612.

D'Angelo R, Marini V, Rinaldi C et al. Mutation analysis of CCM1, CCM2 and CCM3 genes in a cohort of Italian patients with cerebral cavernous malformation. Brain Pathol 2011; 21: 215-224.

D'Angelo VA, De Bonis C., Amoroso R et al. Supratentorial cerebral cavernous malformations: clinical, surgical, and genetic involvement. Neurosurg Focus 2006; 21: e9.

de Oliveira JG, Lekovic GP, Safavi-Abbasi S et al. Supracerebellar infratentorial approach to cavernous malformations of the brainstem: surgical variants and clinical experience with 45 patients. Neurosurgery 2010; 66: 389-399.

De Santis A, Ampollini A, Costa F, Cardia A, Carnini F, Fornari M, Gaini SM, Villani RM. Improvement of preoperative epileptic seizures in patients operated on for cerebral cavernous angioma. Bollettino - Lega Italiana Contro L'Epilessia 2003; 121-122: 139-144.

Denier C, Labauge P, Bergametti F et al. Genotype-phenotype correlations in cerebral cavernous malformations patients. Ann Neurol 2006; 60: 550-556.

Deshmukh V, Albuquerque FC, Spetzler RF. Surgical management of atypical cavernous malformations. Operative Techniques in Neurosurgery 2002; 5: 166-170.

Deshmukh VR, Albuquerque FC, Zabramski JM, Spetzler RF (2003) Surgical management of cavernous malformations involving the cranial nerves. Neurosurgery 53(2):352-357

Di Rocco C, Iannelli A, Tamburrini G. Cavernomas of the central nervous system in children. A report of 22 cases. Acta Neurochir (Wien) 1996; 138: 1267-1274.

Di Rocco C, Iannelli A, Tamburrini G. Cavernous angiomas of the brain stem in children. Pediatr Neurosurg 1997a; 27: 92-99.

Di Rocco C, Iannelli A, Tamburrini G. Surgical management of paediatric cerebral cavernomas. J Neurosurg Sci 1997b; 41: 343-347.

Dodick DW, Cascino GD, Meyer FB. Vascular malformations and intractable epilepsy: outcome after surgical treatment. Mayo Clin Proc 1994; 69: 741-745.

Duckworth EA. Modern management of brainstem cavernous malformations. [Review]. Neurol Clin 2010; 28: 887-898.

Enchev YP, Popov RV, Romansky KV, Marinov MB, Bussarsky VA. Neuronavigated surgery of intracranial cavernomas--enthusiasm for high technologies or a gold standard? Folia Medica (Plovdiv) 2008; 50: 11-17.

Engel Jr. J. Report of the ILAE classification core group. Epilepsia 2006; 47: 1558-1568.

Esposito P, Coulbois S, Kehrli P et al. [Place of the surgery in the management of brainstem cavernomas. Results of a multicentric study]. [French]. Neuro-Chirurgie 2003; 49: 5-12.

Fahlbusch R, Strauss C. [Surgical significance of cavernous hemangioma of the brain stem]. [German]. Zentralbl Neurochir 1991; 52: 25-32.

Faria MP, Fagundes-Pereyra WJ, Carvalho GT, Sousa AA. [Cavernous malformations: surgical management in Belo Horizonte Santa Casa Hospital]. [Portuguese]. Arq Neuropsiquiatr 2004; 62: 1079-1084.

Farmer J-P, Cosgrove GR, Villemure J-G, Meagher-Villemure K, Tampieri D, Melanson D. Intracerebral cavernous angiomas. Neurology 1988; 38: 1699-1704.

Ferroli P, Casazza M, Marras C, Mendola C, Franzini A, Broggi G. Cerebral cavernomas and seizures: a retrospective study on 163 patients who underwent pure lesionectomy. Neurol Sci 2006; 26: 390-394.

Ferroli P, Sinisi M, Franzini A, Giombini S, Solero CL, Broggi G. Brainstem cavernomas: long-term results of microsurgical resection in 52 patients. Neurosurgery 2005; 56: 1203-1212.

Flemming KD, Link MJ, Christianson TJ, Brown RD Jr. Prospective hemorrhage risk of intracerebral cavernous malformations. Neurology 2012; 78: 632-636.

Flickinger JC, Kondziolka D, Pollock BE, Lunsford LD. Radiosurgical management of intracranial vascular malformations. Neuroimaging Clin N Am 1998; 8: 483-492.

Frim DM, Zec N, Golden J, Scott RM. Immunohistochemically identifiable tissue plasminogen activator in cavernous angioma: mechanism for re-hemorrhage and lesion growth. Pediatr Neurosurg 1996; 25: 137-141.

Frischer JM, Pipp I, Stavrou I et al. Cerebral cavernous malformations: congruency of histopathological features with the current clinical definition. J Neurol Neurosurg Psychiatry 2008; 79: 783-788.

Fritschi JA, Reulen HJ, Spetzler RF, Zabramski JM. Cavernous malformations of the brain stem. A review of 139 cases. Acta Neurochir (Wien) 1994; 130: 35-46.

Gamrot J, Bazowski P, Rudnik A, Zawadzki T. [Cavernous angiomas in the Department of Neurosurgery in Katowice]. [Polish]. Wiad Lek 2005; 58: 595-597.

Garrett M, Spetzler RF. Surgical treatment of brainstem cavernous malformations. Surg Neurol 2009; 72 Suppl 2: S3-S9.

Ghannane H, Khalil T, Sakka L, Chazal J. [Analysis of a series of cavernomas of the central nervous system: 39 non operated cases, 39 operated cases, 1 dead]. [French]. Neuro-Chirurgie 2007; 53: 217-222.

Giliberto G, Lanzino DJ, Diehn FE, Factor D, Flemming KD, Lanzino G. Brainstem cavernous malformations: anatomical, clinical, and surgical considerations. [Review]. Neurosurg Focus 2010; 29: E9.

Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. Br Med J 2007; 334: 349-351.

Goel A, Muzumdar DP, Nitta J. Surgery on lesions involving cavernous sinus. J Clin Neurosci 2001; 8 Suppl 1: 71-77.

Gralla J, Ganslandt O, Kober H, Buchfelder M, Fahlbusch R, Nimsky C. Image-guided removal of supratentorial cavernomas in critical brain areas: Application of neuronavigation and intraoperative magnetic resonance imaging. Minim Invasive Neurosurg 2003; 46: 72-77.

Gross BA, Batjer HH, Awad IA, Bendok BR. Brainstem cavernous malformations. Neurosurgery 2009a; 64: E805-E818.

Gross BA, Batjer HH, Awad IA, Bendok BR. Cavernous malformations of the basal ganglia and thalamus. Neurosurgery 2009b; 65: 7-18.

Grunert P, Charalampaki K, Kassem M, Boecher-Schwarz H, Filippi R, Grunert P, Jr. Frame-based and frameless stereotaxy in the localization of cavernous angiomas. Neurosurg Rev 2003; 26: 53-61.

Hahn M, Aschoff A, Kunze S. 667 histologically verified cavernous haemangiomas of the CNS : review of localisation, symptoms and signs, diagnosis and results of operative treatments. Adv Neurosurg 1991; 19: 123-126.

Hammen T, Romstock J, Dorfler A, Kerling F, Buchfelder M, Stefan H. Prediction of postoperative outcome with special respect to removal of hemosiderin fringe: a study in patients with cavernous haemangiomas associated with symptomatic epilepsy. Seizure 2007; 16: 248-253.

Hardy PA, Kucharczyk W, Henkelman RM. Cause of signal loss in MR images of old hemorrhagic lesions. Radiology 1990; 174: 549-555.

Hasegawa T, McInerney J, Kondziolka D, Lee JY, Flickinger JC, Lunsford LD. Long-term results after stereotactic radiosurgery for patients with cavernous malformations. Neurosurgery 2002; 50: 1190-1197.

Hauck EF, Barnett SL, White JA, Samson D. Symptomatic brainstem cavernomas. Neurosurgery 2009; 64: 61-70.

Henninger N, Ahmad N, Morris JG. Intravenous thrombolysis in a patient with known cavernous malformation: a first case report. Am J Emerg Med 2010; 28: 117.e1–117.e3.

Houtteville JP. The surgery of cavernomas both supra-tentorial and infra-tentorial. Adv Tech Stand Neurosurg 1995; 22: 185-259.

Houtteville JP. Brain cavernoma: a dynamic lesion. Surg Neurol 1997; 48: 610-614.

Hsu PW, Chang CN, Tseng CK et al. Treatment of epileptogenic cavernomas: surgery versus radiosurgery. Cerebrovasc Dis 2007; 24: 116-120.

Huang AP, Chen JS, Yang CC et al. Brain stem cavernous malformations. J Clin Neurosci 2010; 17: 74-79.

Huang YC, Tseng CK, Chang CN, Wei KC, Liao CC, Hsu PW. LINAC radiosurgery for intracranial cavernous malformation: 10-year experience. Clin Neurol Neurosurg 2006; 108: 750-756.

Huo L, Wu L, Zhang MY, Hou YH, Ding XP, Fang JS. [Electrocorticography monitoring in microsurgical treatment of solitary cavernous angiomas]. [Chinese]. Zhong Nan da Xue Xue Bao 2008; Yi Xue Ban = Journal of Central South University. Medical Sciences. 33: 448-451.

Iakovlev G, Devaux B, Ghossoub M, Beuvon F, Brami F, Roux FX. [Cerebral cavernomas, epilepsy and seizures. Natural history and therapeutic strategy]. [French]. Neuro-Chirurgie 2005; 51: 3-14.

Jackowski A, Symon L, Bills D. Microsurgical excision of pontomedullary cavernous haemangiomas. J Neurol Neurosurg Psychiatry 1992; 55: 79.

Josephson CB, Leach JP, Duncan R, Roberts RC, Counsell CE, Al-Shahi Salman R; Scottish Audit of Intracranial Vascular Malformations (SAIVMs) steering committee and collaborators. Seizure risk from cavernous or arteriovenous malformations: Prospective population-based study. Neurology 2011; 76: 1548-54.

Jovanovic V, Tasi G, Djurovi B, Janiijevi M, Antunovi V. [Predictive factors for recurrent haemorrhagies in patients with brain cavernoma]. [Serbian]. Acta Chirurgica Iugoslavica 2005; 52: 83-86.

Jovanovic VT, Tasic GM, Djurovic BM et al. [Results of surgical treatment of patient with supratentorial cavernoma and epilepsy]. [Serbian]. Acta Chirurgica Iugoslavica 2008a; 55: 137-140.

Jovanovic VT, Tasic GM, Djurovic BM et al. [Results of the surgical treatment of patients with brain cavernoma that manifested by intracerebral hemorrhage]. [Serbian]. Acta Chirurgica Iugoslavica 2008b; 55: 129-132.

Kameyama S, Kakita A. [Magnetic resonance imaging and pathology in epilepsy (5). Cavernous angioma and arteriovenous malformation]. [Japanese]. No Shinkei Geka 2007; 35: 1199-1206.

Kang BK, Na DG, Ryoo JW, Byun HS, Roh HG, Pyeun YS. Diffusion-weighted MR imaging of intracerebral hemorrhage. Korean J Radiol 2001; 2: 183-191.

Karlsson B, Kihlstrom L, Lindquist C. Radiosurgery for cavernous malformations. J Neurosurgery 1998; 88: 293-297.

Kayali H, Sait S, Serdar K, Kaan O, Ilker S, Erdener T. Intracranial cavernomas: analysis of 37 cases and literature review. Neurol India 2004; 52: 439-442.

Khalil T, Lemaire JJ, Chazal J, Verrelle P. [Role of radiosurgery in the management of intracranial cavernomas. Review of the literature]. Neurochirurgie 2007; 53: 238-242.

Khouri S, Lacerda LP, Guarnieri J et al. [Surgical treatment of cortical and subcortical cavernomas. General principles and personal series of 20 cases treated between 2000 and 2006]. [French]. Neuro-Chirurgie 2007; 53: 163-167.

Kida Y, Kida Y. Radiosurgery for cavernous malformations in basal ganglia, thalamus and brainstem. Progress in Neurological Surgery 2009; 22: 31-37.

Kida Y, Kobayashi T, Mori Y. Radiosurgery of angiographically occult vascular malformations. Neurosurg Clin N Am 1999; 10: 291-303.

Kida Y, Kobayashi T, Tanaka T. Treatment of symptomatic AOVMs with radiosurgery. Acta Neurochir Suppl 1995a; 63: 68-72.

Kida Y, Kobayashi T, Tanaka T, Oyama H, Iwakoshi T. Gamma-radiosurgery of angiographically occult vascular malformations. Japanese Journal of Neurosurgery 1995b; 4: 239-245.

Kidwell CS, Wintermark M. Imaging of intracranial haemorrhage. Lancet Neurology 2008; 7: 256-267.

Kim DG, Choe WJ, Paek SH et al. Radiosurgery of intracranial cavernous malformations. Acta Neurochir (Wien) 2002; 144: 869-878.

Kim MS, Pyo SY, Jeong YG, Lee SI, Jung YT, Sim JH. Gamma knife surgery for intracranial cavernous hemangioma. J Neurosurg 2005; 102 Suppl: 102-106.

Kivelev J, Niemela M, Kivisaari R, Dashti R, Laakso A, Hernesniemi J. Long-term outcome of patients with multiple cerebral cavernous malformations. Neurosurgery 2009; 65: 450-455.

Kloet A, Carpay JA, Wurzer JA. [Cavernous cerebral angioma: indications for neurosurgical removal]. [Dutch]. Ned Tijdschr Geneeskd 1996; 140: 2494-2498.

Kobayashi E, Bagshaw AP, Gotman J, Dubeau F. Metabolic correlates of epileptic spikes in cerebral cavernous angiomas. Epilepsy Res 2007; 73: 98-103.

Komotar RJ, Mikell CB, McKhann GM. "Epilepsy surgery" versus lesionectomy in patients with seizures secondary to cavernous malformations. Clin Neurosurg 2008; 55: 101-107.

Kondziolka D, Flickinger JC, Lunsford LD. Radiosurgery for cavernous malformations. Progress in Neurological Surgery 2007; 20: 220-230.

Kondziolka D, Lunsford LD, Coffey RJ, Bissonette DJ, Flickinger JC. Stereotactic radiosurgery of angiographically occult vascular malformations: Indications and preliminary experience. Neurosurgery 1990; 27: 892-900.

Kondziolka D, Lunsford LD, Flickinger JC, Kestle JR. Reduction of hemorrhage risk after stereotactic radiosurgery for cavernous malformations. J Neurosurg 1995; 83: 825-831.

Kraemer DL, Awad IA. Vascular malformations and epilepsy: clinical considerations and basic mechanisms. Epilepsia 1994; 35 Suppl 6: S30-S43.

Kuncz A, Horvath Z, Bodosi M, Kver F, Doczi T. [Cavernous angioma of the central nervous system]. [Hungarian]. Orv Hetil 1994; 135: 1571-1577.

Labauge P, Denier C, Bergametti F, Tournier-Lasserve E. Genetics of cavernous angiomas. Lancet Neurology 2007; 6: 237-244.

Lapras C, Gharbi S, Mottolese C. The surgical treatment of angiomas in children. Pediatrie (Bucur) 1990; 45 Suppl: s231-s237.

Lapras C, Lapras C, Deruty R, Patet JD, Mottolese C. Surgical treatment of intracerebral cavernomas. Neurochirurgie 1989; 35: 120-125.

Lerch K-D, Schaefer D, Palleske H. Stereotactic microresection of small cerebral vascular malformations (SCVM). Acta Neurochir (Wien) 1994; 130: 28-34.

Lewis AI, Van Loveren HR, Tew Jr JM. Management of brain-stem vascular malformations: Advances in surgical technique and long-term results. Neurosurg Q 1995; 5: 217-228.

Li H, Ju Y, Cai BW, Chen J, You C, Hui XH. Experience of microsurgical treatment of brainstem cavernomas: report of 37 cases. Neurol India 2009; 57: 269-273.

Li X-J, Wan J-H, Li C-Y, Zhao J-Z. Surgical treatment of lateral sellar compartment cavernoma. National Medical Journal of China 2007; 87: 868-871.

Liscak R, Vladyka V, Simonova G, Vymazal J, Novotny Jr J. Gamma knife surgery of brain cavernous hemangiomas. J Neurosurg 2005; 102 Suppl: 207-213.

Liscak R, Vladyka V, Simonova G, Vymazal J, Novotny J, Jr. Gamma knife radiosurgery of the brain stem cavernomas. Minim Invasive Neurosurg 2000; 43: 201-207.

Liu A, Wang CC, Dai K. [Gamma knife radiosurgery for cavernous malformations]. [Chinese]. Acta Academiae Medicinae Sinicae 2005; 27: 18-21.

Lonjon M, Roche JL, George B et al. [Intracranial cavernoma. 30 cases]. [French]. Presse Med 1993; 22: 990-994.

Luccarelli G, Fornari M, Moise A et al. [Intracranial vascular malformations in childhood. Arteriovenous angiomas and cavernous angiomas. Considerations on a series of 37 cases treated surgically]. [Italian]. Riv Neurobiol 1981; 27: 509-519.

Lunardi P, Acqui M. The echo-guided removal of cerebral cavernous angiomas. Acta Neurochir (Wien) 1993; 123: 113-117.

Lunsford LD, Khan AA, Niranjan A, Kano H, Flickinger JC, Kondziolka D. Stereotactic radiosurgery for symptomatic solitary cerebral cavernous malformations considered high risk for resection. J Neurosurg 2010; 113: 23-29.

Maesawa S, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for management of deep brain cavernous malformations. Neurosurg Clin N Am 1999; 10: 503-511.

Mahla K, Rizk T, Fischer C, Belliard H, Vallee B, Fischer G. [Intracranial cavernoma. Surgical results of 47 cases]. [French]. Neuro-Chirurgie 1999; 45: 286-292.

Mao Y, Zhou L, Du G, Chen L. [Image-guided microsurgery in resection of intracranial cavernous hemangioma]. [Chinese]. Chung Hua I Hsueh Tsa Chih 2002; 82: 222-224.

Mathiesen T, Edner G, Kihlstrom L. Deep and brainstem cavernomas: A consecutive 8-year series. J Neurosurg 2003; 99: 31-37.

Mehdorn HM, Barth H, Buhl R, Nabavi A, Weinert D. Intracranial cavernomas: indications for and results of surgery. Neurol Med Chir (Tokyo) 1998; 38 Suppl: 245-249.

Menzler K, Chen X, Thiel P et al. Epileptogenicity of cavernomas depends on (archi-) cortical localization. Neurosurgery 2010; 67: 918-924.

Miyazawa T, Sure U, Bertalanffy H. [Surgical treatment of brainstem cavernous malformation]. [Japanese]. No Shinkei Geka 2003; 31: 851-866.

Monaco EA, Khan AA, Niranjan A et al. Stereotactic radiosurgery for the treatment of symptomatic brainstem cavernous malformations. [Review]. Neurosurg Focus 2010; 29: E11.

Moran NF, Fish DR, Kitchen N, Shorvon S, Kendall BE, Stevens JM. Supratentorial cavernous haemangiomas and epilepsy: a review of the literature and case series. J Neurol Neurosurg Psychiatry 1999; 66: 561-568.

Morris Z, Whiteley WN, Longstreth WT Jr., Weber F, Lee YC, Tsushima Y, Alphs H, Ladd SC, Warlow C, Wardlaw JM, Al-Shahi Salman R. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. Br Med J 2009; DOI: 10.1136/bmj.b3016.

Nagy G, Razak A, Rowe JG et al. Stereotactic radiosurgery for deep-seated cavernous malformations: a move toward more active, early intervention. Clinical article. J Neurosurg 2010; 113: 691-699.

Nataf F, Roux FX, Devaux B et al. [Brainstem cavernomas: surgical experience at the CH Sainte-Anne general hospital]. [French]. Neuro-Chirurgie 2007; 53: 192-201.

National Institute for Health and Clinical Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2012.

Noto S, Fujii M, Akimura T, Imoto H, Nomura S, Kajiwara K, Kato S, Fujisawa H, Suzuki M. Management of patients with cavernous angiomas presenting epileptic seizures. Surg Neurol 2005; 64: 495-498.

Ohue S, Fukushima T, Kumon Y, Ohnishi T, Friedman AH. Surgical management of brainstem cavernomas: selection of approaches and microsurgical techniques. Neurosurg Rev 2010; 33: 315-322.

Ojemann RG, Ogilvy CS. Microsurgical treatment of supratentorial cavernous malformations. Neurosurg Clin N Am 1999; 10: 433-440.

Pfisterer W, hlbauer M, Kleinpeter G, Knosp E. Microsurgical removal of the brain stem cavernoma. Journal fur Neurologie, Neurochirurgie und Psychiatrie 2002; 3: 42-44.

Pinker K, Stavrou I, Knosp E, Trattnig S. Are cerebral cavernomas truly nonenhancing lesions and thereby distinguishable from arteriovenous malformations? MRI findings and histopathological correlation. Magnetic Resonance Imaging 2006; 24: 631-637.

Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. J Neurosurg 1997; 87: 190-197.

Porter R, Zabramski JM, Lanzino G, Feiz-Erfan I, Spetzler RF. Surgical treatment of brain stem cavernous malformations. Operative Techniques in Neurosurgery 2002; 5: 185-190.

Porter RW, Detwiler PW, Spetzler RF. Surgical technique for resection cavernous malformations of the brain stem. Operative Techniques in Neurosurgery 2000; 3: 124-130.

Porter RW, Detwiler PW, Spetzler RF et al. Cavernous malformations of the brainstem: experience with 100 patients. J Neurosurg 1999; 90: 50-58.

Pozzati E, Zucchelli M, Marliani AF, Riccioli LA. Bleeding of a familial cerebral cavernous malformation after prophylactic anticoagulation therapy. Case report. Neurosurg Focus 2006; 21: e15.

Regis J, Bartolomei F, Kida Y et al. Radiosurgery for epilepsy associated with cavernous malformation: retrospective study in 49 patients. Neurosurgery 2000; 47: 1091-1097.

Reich P, Winkler J, Straube A, Steiger HJ, Peraud A. Molecular genetic investigations in the CCM1 gene in sporadic cerebral cavernomas. Neurology 2003; 60: 1135-1138.

Rigamonti D, Drayer BP, Johnson PC, Hadley MN, Zabramski J, Spetzler RF. The MRI appearance of cavernous malformations (angiomas). J Neurosurg 1987; 67: 518-524.

Rohde V, Berns E, Rohde I, Gilsbach JM, Ryang YM. Experiences in the management of brainstem hematomas. Neurosurg Rev 2007; 30: 219-223.

Rougier A, Castel JP, Cohadon F. [Different modalities for the treatment of hemispheric cavernomas]. [French]. Neuro-Chirurgie 1989; 35: 115-119.

Rowe J. Late Neoplastic Complications After Radiation Treatments for Benign Intracranial Tumors. Neurosurg Clin N Am 2006; 17: 181-185.

Ryvlin P, Mauguiere F, Sindou M, Froment JC, Cinotti L. Interictal cerebral metabolism and epilepsy in cavernous angiomas. Brain 1995; 118: 677-687.

Samii M, Eghbal R, Carvalho GA, Matthies C. Surgical management of brainstem cavernomas. J Neurosurg 2001; 95: 825-832.

Savoiardo M, Strada L, Passerini A. Intracranial cavernous hemangiomas: neuroradiologic review of 36 operated cases. Am J Neuroradiol 1983; 4: 945-950.

Schefer S, Valavanis A, Wichmann W. [MRT morphology and classification of cerebral cavernomas]. [German]. Radiologe 1991; 31: 283-288.

Scheuerle AF, Steiner HH, Kolling G, Kunze S, Aschoff A. Treatment and long-term outcome of patients with orbital cavernomas. Am J Ophthalmol 2004; 138: 237-244.

Scottish Intercollegiate Guidelines Network. Diagnosis and Management of Epilepsy in Adults, Section 3: Treatment. 2005.

Secchi P, Calloni MV, Freschi R, Giorgetti A, Mariani G, Morini R, Perrone P, Piazza I, Zancaner F. Epilepsy and cerebral vascular malformations: Retrospective study of 71 cases. Bollettino - Lega Italiana Contro L'Epilessia 1998; 102-103: 111-113.

Shalek PA, Vinogradov BM, Pozdniakov AV et al. [Methods and results of stereotactic radiosurgery for cavernous angiomas]. [Russian]. Voprosy Onkologii 2008; 54: 525-528.

Sheehan J, Schlesinger D. Editorial. Radiosurgery and cavernous malformations. J Neurosurg 2010; 113: 689-690.

Shih YH, Pan DH. Management of supratentorial cavernous malformations: craniotomy versus gammaknife radiosurgery. Clin Neurol Neurosurg 2005; 107: 108-112.

Smith KA, Javedan S, Zabramski JM, Blum DE, Spetzler RF. Cavernous malformations presenting with seizures: Therapeutic options and outcome. Operative Techniques in Neurosurgery 2002; 5: 161-165.

St George EJ, Perks J, Plowman PN. Stereotactic radiosurgery XIV: The role of the haemosiderin 'ring' in the development of adverse reactions following radiosurgery for intracranial cavernous malformations: A sustainable hypothesis. Br J Neurosurg 2002; 16: 385-391.

Stavrou I, Baumgartner C, Frischer JM, Trattnig S, Knosp E. Long-term seizure control after resection of supratentorial cavernomas: a retrospective single-center study in 53 patients. Neurosurgery 2008; 63: 888-896.

Stefan H, Hammen T. Cavernous haemangiomas, epilepsy and treatment strategies. Acta Neurol Scand Suppl 2004; 110: 393-397.

Stefan H, Walter J, Kerling F, Blumcke I, Buchfelder M. [Supratentorial cavernoma and epileptic seizures. Are there predictors for postoperative seizure control?]. [German]. Nervenarzt 2004; 75: 755-762.

Steiner L, Karlsson B, Yen CP, Torner JC, Lindquist C, Schlesinger D. Radiosurgery in cavernous malformations: anatomy of a controversy. J Neurosurg 2010; 113: 16-21.

Tarnaris A, Fernandes RP, Kitchen ND. Does conservative management for brain stem cavernomas have better long-term outcome? Br J Neurosurg 2008; 22: 748-757.

Tasic GM, Djurovic BM, Jovanovic VT et al. [Surgical treatment of brain stem cavernoma--current approaches]. [Serbian]. Acta Chirurgica Iugoslavica 2008; 55: 141-149.

The Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. Arch Intern Med 1996; 156: 409-416.

Tomlinson FH, Houser OW, Scheithauer BW et al. Angiographically occult vascular malformations: a correlative study of features on magnetic resonance imaging and histological examination. Neurosurgery 1994; 34: 792-799.

Tsien C, Souhami L, Sadikot A et al. Stereotactic radiosurgery in the management of angiographically occult vascular malformations. International Journal of Radiation Oncology, Biology, Physics 2001; 50: 133-138.

Tu J, Stoodley MA, Morgan MK et al. Different responses of cavernous malformations and arteriovenous malformations to radiosurgery. J Clin Neurosci 2009; 16: 945-949.

Van Gompel JJ, Marsh WR, Meyer FB, Worrell GA. Patient-assessed satisfaction and outcome after microsurgical resection of cavernomas causing epilepsy. Neurosurg Focus 2010; 29: E16.

Van Gompel JJ, Rubio J, Cascino GD, Worrell GA, Meyer FB. Electrocorticography-guided resection of temporal cavernoma: is electrocorticography warranted and does it alter the surgical approach? J Neurosurg 2009; 110: 1179-1185.

Vaquero J, Salazar J, Martinez R, Martinez P, Bravo G. Cavernomas of the central nervous system: clinical syndromes, CT scan diagnosis, and prognosis after surgical treatment in 25 cases. Acta Neurochir (Wien) 1987; 85: 29-33.

Verlaan DJ, Laurent SB, Rouleau GA, Siegel AM. No CCM2 mutations in a cohort of 31 sporadic cases. Neurology 2004a; 63: 1979.

Verlaan DJ, Laurent SB, Sure U et al. CCM1 mutation screen of sporadic cases with cerebral cavernous malformations. Neurology 2004b; 62: 1213-1215.

Vespignani H, Bouilleret V, Taillandier L et al. Cavernous angiomas revealed by epileptic seizures: 57 cases reports. Epilepsies 1994; 6: 97-111.

Vespignani H, Weber M, Bracard S, Lepoire J. Cavernous angiomas and epilepsy. Epilepsies 1989; 1: 7-20.

Vinas FC, Guthikonda M, Diaz FG. Surgical management of cavernous malformations of the brainstem. Neurol Res 2002; 24: 61-72.

von der Brelie C, Schramm J. Cerebral cavernous malformations and intractable epilepsy: the limited usefulness of current literature. Acta Neurochir (Wien) 2011; 153: 249-259.

von Essen C, Rydenhag B, Nystrom B, Mozzi R, van Gelder N, Hamberger A. High levels of glycine and serine as a cause of the seizure symptoms of cavernous angiomas? J Neurochem 1996; 67: 260-264.

Wang C-C, Liu A, Zhang J-T, Sun B, Zhao Y-L. Surgical management of brain-stem cavernous malformations: Report of 137 cases. Surg Neurol 2003; 59: 444-454.

Wang P, Zhang F, Zhang H, Zhao H. Gamma knife radiosurgery for intracranial cavernous malformations. Clin Neurol Neurosurg 2010; 112: 474-477.

Wang S-K, Xu G-B, Zhang Z-Q. Clinical analysis of intracranial cavernous angioma. Chinese Journal of Clinical Oncology 1995; 22: 397-399.

Weber M, Vespignani H, Forlodou P, Picard L, Lepoire J. Epileptic seizures and cavernous angioma: Report of 24 cases. Bollettino - Lega Italiana Contro L'Epilessia 1988; 62-63: 117-118.

Winkler D, Lindner D, Strauss G, Richter A, Schober R, Meixensberger J. Surgery of cavernous malformations with and without navigational support - a comparative study. Minim Invasive Neurosurg 2006; 49: 15-19.

Winkler D, Lindner D, Trantakis C et al. Cavernous malformations--navigational supported surgery. Minim Invasive Neurosurg 2004; 47: 24-28.

Woydt M, Horowski A, Krone A, Soerensen N, Roosen K. Localization and characterization of intracerebral cavernous angiomas by intra-operative high-resolution colour-duplex-sonography. Acta Neurochir (Wien) 1999; 141: 143-151.

Woydt M, Krone A, Soerensen N, Roosen K. Ultrasound-guided neuronavigation of deep-seated cavernous haemangiomas: clinical results and navigation techniques. Br J Neurosurg 2001; 15: 485-495.

Yeon JY, Kim JS, Choi SJ, Seo DW, Hong SB, Hong SC. Supratentorial cavernous angiomas presenting with seizures: surgical outcomes in 60 consecutive patients. Seizure 2009; 18: 14-20.

Yoon PH, Kim DI, Jeon P, Ryu YH, Hwang GJ, Park SJ. Cerebral cavernous malformations: serial magnetic resonance imaging findings in patients with and without gamma knife surgery. Neurol Med Chir (Tokyo) 1998; 38 Suppl: 255-261.

Yun TJ, Na DG, Kwon BJ et al. A T1 hyperintense perilesional signal aids in the differentiation of a cavernous angioma from other hemorrhagic masses. Am J Neuroradiol 2008; 29: 494-500.

Zabramski JM, Wascher TM, Spetzler RF et al. The natural history of familial cavernous malformations: results of an ongoing study. J Neurosurg 1994; 80: 422-432.

Zevgaridis D, van V, V, Ebeling U, Reulen HJ. Seizure control following surgery in supratentorial cavernous malformations: a retrospective study in 77 patients. Acta Neurochir (Wien) 1996; 138: 672-677.

Zhang N, Pan L, Wang BJ, Wang EM, Dai JZ, Cai PW. Gamma knife radiosurgery for cavernous hemangiomas. J Neurosurg 2000; 93: 74-77.

Zhao J, Wang Y, Kang S et al. The benefit of neuronavigation for the treatment of patients with intracerebral cavernous malformations. Neurosurg Rev 2007a; 30: 313-318.

Zhao J-Z, Kang S, Wang S, Zhao Y-L, Wang R. Neuronavigation and electrocorticography monitoring in resection of brain cavernous malformations. Chung Hua I Hsueh Tsa Chih 2005; 85: 224-228.

Zhao Y, Du GH, Wang YF et al. Multiple intracranial cavernous malformations: clinical features and treatment. Surg Neurol 2007b; 68: 493-499.

Guidelines for the management of cerebral cavernous malformations in adults

Cavernoma Alliance UK
Registered charity number: 1114145

Genetic Alliance UK
Registered charity number: 1114195 and in Scotland SC032999

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