



Angioma Alliance Newsletter

December, 2004

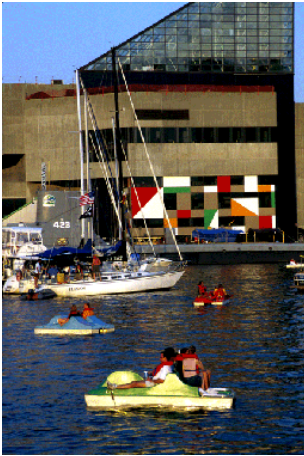
Editor: Connie Lee

In This Issue:

- What's New
 1. Family Conference 2005
 2. Chats
 3. Surgery Support Committee
 4. Pregnancy and Cavernous Malformations
- In the Works:
 1. Cavernous Malformation Patient Registry
 2. Getting Out the Word: New Mexico Genealogy Society Meeting
 3. Where We're Exhibiting
- Don't Forget
 1. Tissue Donation
 2. CCM Awareness Lapel Pin
 3. Igive.com, Barnes And Noble, and MissionFish
- Cerebral Cavernous Malformations and Hemorrhage
- Latest Research:
 1. CCM3 Identification Leads to Speculation about CCM4
 2. Mouse Model is Getting Better
 3. Epilepsy and Surgery Success
 4. Surgery Advances
 5. Functional Imaging Before Surgery

Please note: In this newsletter, the terms "cavernous angioma," "cavernous malformation" and "CCM" are used interchangeably.

What's New?



Family Conference 2005

Save the dates!

Angioma Alliance will be holding its second family conference Friday, June 24th through Sunday, June 26th at the Tremont Plaza Hotel in Baltimore, Maryland.

One highlight of this year's conference will be the opportunity to tour Dr. Daniele Rigamonti's Johns Hopkins cavernous angioma genetics research lab. In addition to Dr. Awad and Dr. Clatterbuck, favorites of last year's conference, we are planning to have speakers from a wider range of disciplines including neurologists and disability specialists. We will also have structured opportunities to hear each other's stories and a panel comprised of Angioma Alliance members discussing surgery experiences and fielding questions.

There will be childcare available during the presentations for kids 13 and under. We are planning a field trip to Port Discovery, the wonderful Baltimore Children's Museum, during the presentations on Saturday.

For more information about Baltimore attractions, visit <http://www.baltimore.org/>.

We'll have more detailed information about registration, costs, and activities in our next newsletter.

Chats

Angioma Alliance now has a chat room! We have been holding scheduled chats approximately every two weeks on various topics. So far, we've covered Brainstem Cavernous Angiomas, Pediatric Medical Issues, Parenting a Child with Cavernous Angioma, and Surgery Issues. The transcripts of these chats can be found through the link on our main menu. Our chats are on a short holiday break right now, but will resume in January.

Topics for next year include Surgery Issues for Spouses and Friends, Disability and Vocational Rehabilitation, and Vision Therapy. If there is a topic you'd like to talk about, please let us know and we will try to set it up.

Surgery Support Committee

We are happy to announce that four volunteers have formed a surgery support committee that has been and will be moderating chats, putting information on the website, and serving as a resource for those with surgery and recovery questions. The volunteers are Kelly (indykelly on the Community Forum), Tasha Scott (tasha.20), and Amy Jagemann (amy). If you would like to contact them, please use the mail or PM feature in the Community Forum. To do this, click on the Members button, and click on the member name. This feature is available also in every Community Forum post made by these individuals.

Angioma Alliance is run entirely by volunteers – if, like Kelly, Tasha, and Amy – you have a desire to become involved in this committee or in any other way, please let us know at info@angiomaalliance.org.



Pregnancy and Cavernous Malformations

Please check our new webpage on [Pregnancy and Cavernous Angioma FAQs](#) to read a very comprehensive guide for those with or without the hereditary form of cavernous angioma who are contemplating pregnancy.

We would like to add a second page to the section entitled [Pregnancy Experiences](#). To do this, we need your help. If you have been through a pregnancy with a cavernous malformation, even if you had no problems or didn't know you had the illness, please share your story with us. We would like to print one or two paragraph entries from as large a number of women as possible so that those visiting this site for the first time can read as wide a range of experiences as possible. Reading the facts is very different from reading the experiences, and we hope our site can offer both. Your submission can remain anonymous or contain any identifying name you like. We'd be grateful if you could send your story to info@angiomaalliance.org or drop it into the mail to us.

In the Works

Patient Registry

The Angioma Alliance Patient Registry continues to work its way toward becoming a reality.

In case you haven't heard, **here's the overview:**

In our most ambitious endeavor to date, we are planning to give our researchers an enormous boost by creating an extensive patient registry, with detailed family, medical history and lifestyle information for thousands of individuals affected by the illness. This is information that folks who visit our online community forum share anecdotally all the time. At this time, it has become clear to researchers that information about the three genes that can cause the hereditary form of the illness does not explain individual variation in the severity of the illness. Our researchers have told us that what is needed is an independent patient registry that they can use to test their hypotheses. This applies both to individuals with the hereditary form of the illness and those with the sporadic form. Knowing what other factors come into play can help to determine the direction of the search for treatment. A patient registry can provide this kind of individual information, potentially reducing the time to treatment by years.

Only Angioma Alliance can do this. The CDC does not have the funding to collect and store information that is this detailed. We are able to gather information not just from the individuals who use our site, but through our relationships with physicians, our own researchers, and people who are receiving clinical genetic testing for the illness.

We will be entering into a co-operative patient registry created by the Genetic Alliance, an umbrella organization for over 600 organizations like ours. By joining their registry, not only do we have access to a \$500,000 software package and professional consulting, but we can form alliances with other organizations to share registries for cross-disease research. The Genetic Alliance projects that



they will have their co-operative in place by July, 2005. This is so important, that we hope to join at the very beginning.

Our registry will also have information relevant to other aspects of the cavernous angioma experience. For example, we would like to understand the efforts people with cavernous angioma had to make to get to a diagnosis so that we can help doctors improve the process.

Here's the news:

Right now, because of the work of our fundraising chair Liz Neuman, we have raised \$7400 that is specifically designated for setting up the registry. During the first year of the project, we will need \$20,000-\$30,000 – we still have a long way to go.

We are developing the form that will be used to collect information from participants. We will be helped in this effort by Dr. Eric Johnson, a member of our Scientific Advisory Board and the Executive Director of the Genetic Alliance registry, and by Dr. Leslie Morrison, a neurologist at the University of New Mexico. Dr. Morrison has assembled a team of professionals including an epidemiologist and a number of vascular specialists to help develop a data collection tool.

What you can do now. If you think you might want to become part of the registry when it is up and running, please let us know. It would be wonderful for us to collect contact information for as many folks as we can so that we can get started quickly. Also, if there are questions that you would like to see a registry address, please send them. Our email address is info@angiomaalliance.org. You are the experts on this illness - we would like to know what you suspect puts a person at higher risk for having a hemorrhage.

Finally, we would be grateful for any contribution you can make to speed up the process of finding real treatments for cavernous angioma. This is the most expensive undertaking we have planned to date. Every contribution makes a difference. If you would like to host a fundraiser, please let us know. We now have a DVD that can be shown at privately hosted events explaining our illness, Angioma Alliance, and the patient registry. And, if you know of any companies or individuals that you think might be willing to underwrite a portion of the patient registry project, please let us know. This is a relatively small investment that will provide a disproportionately large return for our families.

You can contribute by sending a check to Angioma Alliance, 107 Quaker Meeting House Rd., Williamsburg, VA 23188 or by using our Paypal connection. If you would like your contribution to be designated specifically for the patient registry rather than for general operating expenses, please note this in the memo line of your check or in the comments section of your Paypal payment submission.



Getting Out the Word: The New Mexico Genealogy Society

New Mexico has one of the largest concentrations of individuals with the common Hispanic variant of the CCM1 mutation. The story behind this is believed to be as follows: several hundred years ago, a person of Spanish descent who lived in the Southwest before it was part of

the United States developed a hereditary form of cavernous malformation. Among the descendents of this individual there is a common mutation, known as a founder mutation. An individual gene can mutate in countless ways – the members of this extremely extended family all have the exact same mutation on the CCM1 gene. While there are many affected families in New Mexico, there does not seem to be a focus on this by either physicians or public health officials.

Joyce Gonzales, an Angioma Alliance volunteer and affected family member, will begin the process of increasing public awareness of the CCM and the common Hispanic mutation in a presentation she will be giving on January 10th to the New Mexico Genealogy Society. She will

be joined in her presentation by Dr. Leslie Morrison of the University of New Mexico who will discuss the genetics of the disorder in more depth. This is a particularly appropriate group of people to address, since many in the audience will be ancestors of the original Spanish settlers in New Mexico. We want to thank Joyce for taking the time to share her family's story.



Where We Are Exhibiting

As you read in the last newsletter, in April 2004, Angioma Alliance exhibited at the American Academy of Neurology annual convention in San Francisco. This was wonderful exposure for our illness and really underscored the need for increased outreach to the neurology community. While our booth was visited by a number of knowledgeable neurologists, more often we were helping to educate neurologists who knew very little about the illness. It also gave us the opportunity to give the neurologists our informational brochure so that they might pass these on to their patients. We will be returning in April 2005 to continue this work at the AAN convention in Miami. This year we will be fortunate enough to have the presence of board member Norma Villa who will help Spanish-speaking physicians learn about us and our resources.

We will also be exhibiting at the American Academy of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section joint conference with the American Society of Interventional & Therapeutic Neuroradiology in February. The purpose of our participation in this conference is to promote awareness of our organization among cerebrovascular surgeons so that they may refer their patients to our resources and to the research projects of our advisors.

Don't Forget

Tissue Donations

Angioma Alliance is becoming more actively involved in facilitating cavernous angioma tissue donation to research laboratories. Research laboratories have an immediate and long term need for cavernous angioma tissue that has been surgically removed. Currently, labs are using the tissue to gain understanding of the process of cavernous angioma formation and hemorrhage. This is important work that will have an enormous impact on future treatment options for this illness.

Angioma Alliance has published descriptions of the individual research projects in the US that require cavernous angioma tissue on our [Studies Seeking Participants](#) page. We hope this will aid you in choosing a lab to receive your tissue donation. You do not have to have the familial form of the illness to donate. We would like to encourage anyone facing surgery in the US who would like to donate their angioma to call us at our new toll-free number, 1-866-HEAL-CCM, so that we can help to make arrangements. Your donation could make a big difference in the pace of research progress.

CCM Awareness Pins



Our CCM awareness lapel pins are becoming a popular fashion accessory. Like the ribbons associated with other illnesses, our “little red guy” pin is a wonderful way to increase awareness of cerebral cavernous malformation (CCM), our little known illness. Increasing public awareness can go a long way toward increasing research funding and improving the quality of life we all lead. We’re offering the pin as a thank you for any donation of \$10 or more. Each pin comes with 5 cavernous angioma information cards that can be handed to anyone who might have questions.

You can send your donation through the mail to:

Angioma Alliance
107 Quaker Meeting House Road
Williamsburg, VA 23188

Or, you can use the “Make a Donation” link on our home page to donate using a credit card. All donations to Angioma Alliance are tax deductible.

Igive.com, Barnes and Noble, and MissionFish



With holiday season here, there are several ways that you can help Angioma Alliance as you shop. First, do your online shopping through Igive.com. When you use the Igive.com website to shop at your favorite retailers, up to 27% of each purchase you make comes back to us at no additional cost to you. Simply register and select Angioma Alliance as your chosen charity. Then, every time you shop, go to the Igive.com site first and use their links to your favorite retail sites. 587 retailers are listed with them at this time, including almost all major stores. Igive.com also offers coupons and exclusive deals for those who participate.



Second, use the link to Barnes and Noble found on our [Bookstore](#) page each time you access the Barnes and Noble site. 5% of the purchase price of anything you buy at Barnes and Noble during that visit will be donated to Angioma Alliance.



Finally, if you’re selling goodies on Ebay, a way for you to use Ebay to help Angioma Alliance is to register as a seller with [MissionFish](#). This allows you to designate a percentage of the sales price of items you sell as a tax deductible donation to Angioma Alliance. You keep the remaining percentage.

Cerebral Cavernous Malformation and Hemorrhage

By Jack Hoch; Reviewed by Dr. Issam Awad

Background

Although cerebral cavernous malformations (CCMs) have been diagnosed and researched for years, the mechanism by which these lesions hemorrhage remains poorly understood. While there are various theories regarding CCM hemorrhagic behavior, none have been unequivocally proven. Even so, the observed hemorrhage types deserve discussion.

Hemorrhage Types

Since CCMs are low pressure, low flow lesions, there is no clearly understood forcing mechanism which would result in a hemorrhage. Most of the bleeding can be divided into three groups¹:

- 1) "Slow ooze": blood slowly seeps through the cavern "walls" inside the CCM itself. Since the internal cavern walls are very weak, it doesn't take much for blood cells to penetrate them. Normally this does not result in noticeable symptoms, but over time, the lesion's shape or size can change. Almost all CCMs experience this type of oozing.
- 2) Thrombosis: due to the stagnant nature of the blood in the CCM caverns, a thrombus (locally developed blockage/clot) can develop which can cause re-routing of the slow internal blood flow as well as growth inside the lesion. Much like 1) above, most times this is not clinically significant unless the lesion reaches a large enough size to impact surrounding brain tissue.
- 3) Gross hemorrhage: blood escapes the confines of the lesion resulting in the deposit of blood products in normal brain tissue adjacent to the lesion. It is this hemorrhage type that is most commonly associated with overt clinical symptoms. Fortunately, the frequency of this hemorrhage type is lower than either 1) or 2). Symptoms primarily depend upon the exact hemorrhage location in the brain.

Clinical Significance of Hemorrhage and Potential Surgical Implications

For those patients experiencing overt hemorrhage, the sudden onset of disparate symptoms is both confusing and frightening. Many patients demand answers that are not yet available based upon past studies of the natural history of CCMs.

Receiving a CCM diagnosis upon experiencing symptoms is not a death sentence. The majority of lesions don't bleed and the ones that do normally don't explode like bombs. They may leak slowly, but this leakage can be enough to cause symptoms in the tight confines of the brain. There simply isn't enough room to accommodate foreign material such as excess blood. The result is compression or destruction of fragile nerve cells, resulting in the manifested symptoms.

The impact of a hemorrhage depends on its location in the brain. For example, the biggest problem faced by patients who have lesions in the temporal lobe is one of seizures. Hemosiderin, a type of aged blood product that can be deposited in adjacent brain tissue after an overt hemorrhage, is a known irritant. It is enough to cause seizures when found in this location.

Those harboring brainstem lesions normally suffer multiple and diverse symptoms (“focal neurological deficits”) ranging from double vision, nausea, balance problems, swallowing inability, and respiration difficulty among others.

Surgery is normally considered for those patients who have had more than one bleed in conjunction with worsening symptoms. Lesions such as these are normally considered “aggressive” and need to be removed, assuming the lesion is surgically accessible. While recovery from a hemorrhagic event normally occurs, many times a full recovery is not made. Each hemorrhage brings with it additional symptoms which may not resolve.

When considering surgery, pre-surgical patient condition is very important. The better the person’s physical condition prior to surgery, the better the chances of a successful lesion removal and recovery. Neurosurgeons recommend scheduling surgery after varying periods post-bleed, if possible. This allows time for excess blood absorption, unmasking the lesion’s boundary relative to healthy brain tissue; however, if surgery is contemplated, it should not be delayed so long after a bleed that the lesion begins to shrink, making extraction more difficult.

Hemorrhage and Pregnancy

It has not yet been determined whether there is an increased risk of cavernous malformation hemorrhage during pregnancy. Some researchers believe that increased estrogen during pregnancy causes changes in the walls of cavernous malformations in such a way that they are more likely to leak.^{ii,iii} However, there are no clear statistics from large scale studies on whether hemorrhages occur more frequently in pregnant women than in others with cavernous malformations. The vast majority of women complete a pregnancy without a hemorrhage or need for surgical removal of an angioma. However, pregnancy is a time of intense physiologic changes for mother and baby, and the consequences of hemorrhage or seizure may be more complicated than in the non-pregnant state. Any patient with neurovascular problems and/or epilepsy is urged to have their pregnancy overseen by a high risk obstetrician. Your obstetrician should work in close coordination with a neurologist or neurosurgeon that is familiar with your neurological history and who is knowledgeable about cavernous malformations and about epilepsy in pregnancy.

Preventative Measures and Other Considerations

So if you are diagnosed with a lesion, what precautions should you take? What should or shouldn’t you do?

General consensus among neurosurgeons most familiar and experienced with CCMs is that patients harboring a lesion should:

- 1) maintain blood pressure as low in the normal range as possible
- 2) avoid blood thinning or anti-clot medications including aspirin, when possible. This is especially critical for patients whose lesions have demonstrated recent growth or hemorrhage. According to Dr. Issam Awad, chair of the Angioma Alliance scientific board, specific thinners to avoid include Coumadin and aspirin, but also common nonsteroidal antiinflammatory medications such as Advil, Motrin, and the newer Celebrex, Vioxx, etc. While many patients take these medications without problem, it is likely that hemorrhage risk is increased; this could be serious with Coumadin. Pros and cons should be discussed between your doctor and the neurospecialist watching the CCM. In contrast to the above medications, Tylenol (acetaminophen) is a common pain killer that does not cause bleeding tendency. This is recommended for CCM patients.
- 3) stay away from roller coasters or any activity inducing strong gravitational force

- 4) stay stress free. Of course, this is much easier said than done! Dr. Awad notes that stress can alter neurological symptoms after a stroke, and can account for fluctuations of symptoms. There is no known physiologic or hormonal basis for this. However, stress can increase blood pressure, which could be a problem in hypertensive patients with increased hemorrhage risk.

Patients with CCMs can:

- 5) exercise moderately, but avoid strenuous activities such as heavy weightlifting that can cause acute spikes in blood pressure
- 6) give birth vaginally (assuming the patient is female!) as long as the CCM is closely managed during the term of pregnancy
- 7) fly in commercial aircraft with normal cabin pressures
- 8) consume alcohol and caffeinated beverages in moderation

Dr. Awad notes that there has been some relation shown between diet pills, certain stimulants, and nasal decongestants containing phenylpropranolamine and intracranial hemorrhage in young patients, including possibly cases with CCM. These items have been taken off the shelves by the FDA, but it is possible that other excessive stimulants might cause bleeds.

He explains that stimulants may increase blood pressure in hypertensive patients and this could contribute to predisposition to hemorrhagic stroke. Extreme stimulants such as cocaine and other illicit drugs have been shown to cause brain hemorrhages among patients without prior history of high blood pressure, including cases pre-existing vascular malformations.

Summary

Because questions remain regarding the natural history of CCMs, the mechanism by which these lesions hemorrhage and the resultant consequences are not fully understood. The important consideration is that patients can lead long and healthy lives even after a hemorrhagic event. Should symptoms suddenly appear, don't delay in getting an MRI and consulting with a neurosurgeon that has extensive experience managing and treating CCMs. In this case, ignorance is not bliss!

Latest Research Results

By Connie Lee; Reviewed by Douglas Marchuk, Ph.D. and Issam Awad, MD

Following is a summary of the journal articles published since our last newsletter release:

CCM3 identification leads to speculation about CCM4

The French CCM research group, headed by Dr. Tournier-Lasserre, believes they have identified the CCM3 gene. In an article published in the American Journal of Human Genetics, the group had identified 20 families that had either a member with multiple cavernous angiomas or multiply affected family members. These families were tested for the CCM1 or CCM2 mutations and did not have either. Of those 20 families, 8 had the mutation in a gene that is named Programmed Cell Death 10 or PDCD10. PDCD10 had been identified previously in research not related to CCM. The group believes that PDCD10 is the CCM3 gene.^{iv}

One interesting part of this article is that 12 of the 20 families did not have a mutation on this gene. This means that more than half of their participants had a familial mutation that could not be identified. It is appearing possible that there is at least one other gene that can cause familial cavernous malformations that has not yet been identified. So far, two North

Americans labs have reported to us that they have confirmed the PDCD10 mutation as a source of familial cavernous malformation in a very small group of families. The French group's identification appears to be a first chapter in what will likely turn out to be a much larger story.

Mouse model gets better

The Duke University lab has developed a method for consistently producing mice with cavernous malformations. These mice have the mouse version (ortholog) of the human CCM1 mutation. Previously, a genetically altered mouse with the Ccm1 mutation rarely developed a cavernous malformation. The group found that by turning off a second gene, one responsible for tumor suppression known as Trp53, 55% of mice developed lesions. The group speculates that Trp53 may have a direct role in the formation of vascular malformations, but its role in human CCM genesis remains speculative. Nevertheless, the idea of "a second hit", i.e. another genetic predisposition or second mutation beyond the CCM genotype, seems to be supported by this model. Other research pending publication from a North American laboratory has confirmed somatic mutations in a human CCM lesion, i.e. a mutation in cells within a surgically removed cavernous malformation, and this may be another mechanism of "second hit" accounting for at least some human lesions.

Mouse models are an important tool, allowing the study of cavernous malformation formation and evolution over time, and the testing of novel diagnostic and therapeutic paradigms. They also allow the testing of scientific hypotheses regarding mechanisms of lesion genesis, growth and hemorrhage.^v

Epilepsy and surgery success

In a review article, Drs. Stefan and Hammen at the Epilepsy Center in Erlangen, Germany looked at a number of studies of epilepsy caused by cavernous malformations that had been treated with surgery. They found that the earlier the surgery was performed relative to the beginning of seizures, the more likely it was to be successful. This is believed to be true generally because each bleed in a cavernous angioma deposits more hemosiderin, which may increase seizure activity. There is a range of surgery success rates depending on the study. The percent of patients who became completely seizure free or had a dramatic reduction in number of seizures after surgery was 60-92%, depending on the study - most studies showed substantial improvements in 80%+ of patients.^{vi}

Surgery Advances

Surgery to remove cavernous malformations in a part of the brain called the left insula has been very challenging. The insula is under the frontal, parietal, and temporal lobes in the brain, making it difficult to access without impacting functions controlled by these lobes. Also, the area itself plays a crucial role in coordinating the autonomic nervous system, in language acquisition and production, in memory, and in smell. A case study presented by a surgeon in France reports a successful surgery in the left insula that was performed while the patient was awake using both neuronavigation (which helps to locate the site of the cavernous malformation) and functional mapping. The patient's seizure disorder was resolved by the surgeon. This surgeon suggests that surgery in the left insula be considered routinely with the assistance of neuronavigation and functional mapping.^{vii}

Functional Imaging before Surgery

Functional MRI can be used to map a function, like speech, to a specific area of an individual's brain. This technology is used occasionally before cavernous malformation surgery to help the surgeon identify areas of the brain to be avoided. A recent study indicates that functional MRI using blood oxygen level dependent contrast, the most commonly used form of functional MRI, is less accurate with cavernous malformations than with other types of vascular malformations. Cavernous malformations can appear larger than they really are because of hemosiderin deposits left by previous bleeds. This may lead a surgeon to overestimate the size of the safe area in which to operate.^{viii} As this is a very new finding, if you are scheduled for a functional MRI before surgery, it might be wise to ask your surgeon if he or she is familiar with this study.

In seizure disorders involving cavernous malformations, surrounding brain tissue may be involved in causing seizure activity. In performing surgery to remove a cavernous malformation in order to eliminate a seizure disorder, the surgeon must remove all of the "epileptogenic" tissue in order to be successful. A research group in Germany has been using magnetoencephalography (MEG) successfully to identify the boundaries of the epileptic zone. MEG is a technology, like PET scan and functional MRI, which can produce a picture of the brain's functioning, not just its anatomy.^{ix} However, it must be emphasized that there is no evidence that resection of additional brain tissue beyond hemosiderin stained gliosis near the lesion will contribute to improved seizure control. Most patients with seizures proven related to a single CCM lesion will have dramatic improvements in seizures after lesion resection alone. More extensive "seizure surgery", resecting brain outside the CCM lesion, can be considered in the few patients who fail more limited operation.

ⁱ Barrow, DL and Krisht, Ali. Cavernous Malformations and Hemorrhage. *Cavernous Malformations*. 1993:70.

ⁱⁱ [Pozzati E, Acciarri N, Tognetti F, Marliani F, Giangaspero F](#). Growth, subsequent bleeding, and de novo appearance of cerebral cavernous angiomas. *Neurosurgery*. 1996 Apr; 38(4):662-9; discussion 669-70.

ⁱⁱⁱ [Perez Lopez-Fraile I, Tapiador Sanjuan MJ, Eiras Ajuria J, Gimenez Mas JA](#). [Cerebral cavernous angiomas in pregnancy. Two cases and a review of literature] *Neurologia*. 1995 Jun-Jul; 10(6):242-5. Spanish.

^{iv} [Bergametti F, Denier C, Labauge P, Arnoult M, Boetto S, Clanet M, Coubes P, Echenne B, Ibrahim R, Irthum B, Jacquet G, Lonjon M, Moreau JJ, Neau JP, Parker F, Tremoulet M, Tournier-Lasserre E, Societe Francaise de Neurochirurgie](#). Mutations within the Programmed Cell Death 10 Gene Cause Cerebral Cavernous Malformations. *Am J Hum Genet*. 2004 Nov 12; 76(1) [Epub ahead of print]

^v [Plummer NW, Gallione CJ, Srinivasan S, Zawistowski JS, Louis DN, Marchuk DA](#). Loss of p53 sensitizes mice with a mutation in *Ccm1* (KRIT1) to development of cerebral vascular malformations. *Am J Pathol*. 2004 Nov; 165(5):1509-18.

^{vi} [Stefan H, Hammen T](#). Cavernous haemangiomas, epilepsy and treatment strategies. *Acta Neurol Scand*. 2004 Dec; 110(6): 393-7.

^{vii} [Duffau H, Fontaine D](#). Successful resection of a left insular cavernous angioma using neuronavigation and intraoperative language mapping. *Acta Neurochir (Wien)*. 2004 Aug 30.

^{viii} [Thickbroom GW, Byrnes ML, Morris IT, Fallon MJ, Knuckey NW, Mastaglia FL](#). Functional MRI near vascular anomalies: comparison of cavernoma and arteriovenous malformation. *J Clin Neurosci*. 2004 Nov; 11(8):845-8.

^{ix} [Stefan H, Scheler G, Hummel C, Walter J, Romstock J, Buchfelder M, Blumcke I](#). Magnetoencephalography (MEG) predicts focal epileptogenicity in cavernomas. *J Neurol Neurosurg Psychiatry*. 2004 Sep; 75(9):1309-13