



Angioma Alliance Newsletter

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

Updates

Family Conference 2004

The weekend of June 11-13, Angioma Alliance hosted its first family conference in Skokie, Illinois near Chicago. Thirty-three family members plus their children participated in a weekend of activities. We got to know each other during the Friday evening reception, Saturday dinner, and Sunday picnic. It was wonderful to be able to put faces with stories.



Saturday was devoted to presentations by the leading researchers in the field. In the morning, participants learned the basics of cavernous malformation symptoms, treatment



decision-making, new technologies for surgery and imaging, and rehabilitation. In the afternoon, we were challenged by research presentations covering the latest in genetic (see the photo on the left of Dr. Doug Marchuk presenting genetic basics) and micro-biological research.

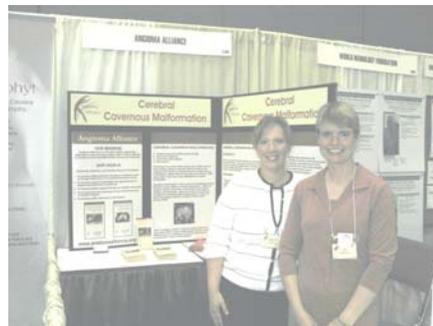
One upshot of the conference was the announcement that, for the first time, researchers will hold their own scientific meeting this September. They will be discussing ways in which they might be able to collaborate to speed the pace of research. We are very proud that our event helped to further these relationships.

You can find the PowerPoint presentations that were shown on Saturday and additional photos of the event by following the link from our home page. We are still working on converting and editing the video, but should have it available shortly.

Next Year: Next year's conference will be held June 24-26 in Baltimore, MD. We will provide more details as our planning continues.

AAN Convention

In April, 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 hope to return to the convention next year, as funds allow, in order to continue this very important work. Please see our "Neurologist Awareness" article below to learn about the other important ways we will expand our efforts in this area.

We also plan to exhibit 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.

Ebay Celebrity Auction

During the week of May 9, Angioma Alliance held its annual Ebay Celebrity and Sports Auction. So far this year, we have raised more than \$800 through this event. The item that received the highest bid was a script from the TV show "West Wing" autographed by Martin Sheen that sold for \$304. We have received a number of other items since the auction closed and will put these up for bid in September. We are very grateful for the support we have received over the last two years from our celebrity donors.

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 donation to Angioma Alliance. You keep the remaining percentage.

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" button on our home page to donate using a credit card. All donations to Angioma Alliance are tax deductible.

What's New

Chat Room

Angioma Alliance now has a chat room! We will be holding scheduled chats approximately every two weeks on various topics. Our first chat will be on Sunday, August 22 at 8:30 pm EDT (7:30 pm Central, 6:30 pm Mountain, and 5:30 pm Pacific, 0130 Greenwich Mean Time) on the topic of brainstem cavernous malformations. Jack Hoch from the Angioma Alliance Board of Directors will be moderating the chat.

What is even more exciting about this new feature is that we will use the chats to develop a list of questions that will be sent out to clinical experts after the chat. For brainstem cavernous angiomas, we are expecting the leading cerebrovascular surgeons in the US to participate in bringing answers back to you. This is a great opportunity to learn more about brainstem cavernous angiomas and to share stories with others.

In the future, we will hold chats about numerous other topics, including surgery recovery issues, pediatric cavernous angioma, disability issues, pregnancy and cavernous angioma, a chat for individuals under 25 with the illness, and a Spanish chat.

Clinical Genetic Testing

As most of you know, there are two forms of the cavernous malformation disease: sporadic and familial. The familial, or hereditary, form of the illness is distinct in several ways. It is passed on in an "autosomal dominant" way, meaning that each child of a person with the familial form has a 50% chance of inheriting the illness. Secondly, the familial form often is characterized by multiple lesions. Many people are interested in finding out if they have the familial form using genetic testing.

There are two types of testing for genetic mutations that can cause the familial form: research testing and clinical testing. Because of its strict regulation, clinical testing can be used to make a diagnosis of a genetic mutation. Research testing (that which you get when you enroll in a study) must be verified by a clinical test before it is considered to be a formal diagnosis.

At this time, there is only one laboratory in the USA that is approved to perform clinical testing of the CCM1 and CCM2 genes. This is Prevention Genetics, a for-profit laboratory directed by Eric Johnson, Ph.D., one of our scientific advisors. The link that follows describes the testing that is offered, the requirements for samples, and the costs involved. The informational pages are written for your lab or doctor's office in the event that you would like to send a blood sample for testing.

Unfortunately, at this time, the CCM3 gene has not yet been identified so genetic testing is not yet available for this mutation. CCM3 is thought to cause about 40% of familial cavernous angioma.

You can find more information on our site at http://www.angiomaalliance.org/Clinical_Testing.html

To contact Prevention Genetics directly:

Dr. Eric Johnson
Director, Molecular Diagnostics and BioBanking
Prevention Genetics
eric.johnson@preventiongenetics.com
Contact: 715-387-0484

New Board Member



We are pleased to announce the addition of Amy Jagemann to the Angioma Alliance Board of Directors. Amy was diagnosed with a cavernous angioma of the basal ganglia in 2002. Her primary symptom was debilitating headaches. After several doctors' visits and a few opinions, she was diagnosed. At this point, she is believed to have the sporadic form of the illness. She had surgery to remove her CA on 6/11/02, just 6 weeks before her wedding. Amy has made a complete recovery since the operation. She works full-time as a Sales Analyst and is working toward a Master's in Business Administration. Amy will be helping Angioma Alliance with public awareness and event planning.

Fund-Raising Committee

As Angioma Alliance grows in services and in the numbers of individuals who participate, our need for formal committees is also growing. Our first committee is a fund-raising committee, chaired by Liz Neuman, a parent of two sons with multiple cavernous angiomas. Current members of the committee are Tori Smalley, Ann Bartelt, and Karen Weber. They are exploring ways to raise money for Angioma Alliance through events and appeals. We are very

excited that they have taken on this vital work. Our hopes for the future are enormous and important, as you will read below, and Liz's committee is a vital part of making these hopes come true. If you would like to join the committee, please contact us at info@angiomaalliance.org.

Even if you do not join the committee, we would like to encourage you to join us in writing letters to family and friends asking for support for Angioma Alliance. We have template letters that you can personalize, and we will provide brochures, envelopes, etc. to send along with your appeal. Personal letters have been our major source of funding since we started – it is our family and friends that care most about us and our illness. Our letters are also a way to help others to understand cavernous angioma, the challenges we face, and the work of Angioma Alliance.

Portuguese Translation

About one month ago, we received a submission for our Stories section from a Brazilian man named Roberto de Cillo. In addition to sharing his experiences, Roberto was very interested in helping to bring our information to the 170 million Portuguese-speaking people around the world. We have already translated our website and brochure into Spanish, with good response. Very generously, Roberto offered to assist us in translating our site and brochure into Portuguese. Coincidentally, we received an email last week from Dr. Jorge Marcondes de Souza, a neurosurgeon who is the head of a cavernous angioma research lab in Rio de Janeiro. He also has offered to help develop a Portuguese version of our site with information that is particular to Brazilian medical resources. He and Roberto de Cillo will be working together to make a Portuguese site a reality. We are very excited about this opportunity to reach out to an ever-expanding international community.

Our Future Plans

Cavernous Malformation Patient Registry

With your support and participation, Angioma Alliance's involvement with research may expand dramatically by next summer. Through the Genetic Alliance (www.geneticalliance.org), we will have the opportunity to create a comprehensive patient registry to collect and store all of the important medical, family history, and lifestyle information about individuals with cavernous malformations.

This database would allow researchers to search out similarities and answer some of the most important questions about individual variation in the illness. For example, they could compare family medical histories to see whether a family history of an auto-immune disorder happens more often in those who have more hemorrhages. Or, we may be able to track whether life events like flying, increased stress, or viral infections have any relationship to hemorrhage. With the help of our researchers, we may even be able to match most of the database information with a blood sample from those who participate. There will be some obvious limitations to our data since we will likely not encounter many participants who have a cavernous malformation but have no symptoms. However, the information that we will be able to offer to research is invaluable and could reduce the time to a better treatment for cavernous malformation by years.

We are in the planning stages of this project. We will be working with our researchers, the Genetic Alliance, clinicians, and you to iron out the details of what information is most important to collect, how we will enroll participants, and how best to maintain the confidentiality of our participants.

We will be seeking funding from various sources, as this is a project that will cost in the tens of thousands of dollars. As you can imagine, this is a drop in the bucket in terms of total cavernous malformation research funding, but it is a huge financial undertaking for us. We feel justified in pursuing an expensive project because Angioma Alliance is the only entity that can create this registry. We are unique in that we are the only organization, public or private,

to have a relationship with both the research community and with families/individuals affected by the illness. If we don't create the registry, it will not be created.

Your participation in this project is vital. At this point, you can help by sending the questions that you would like to have answered by researchers to info@angiomaalliance.org. Eventually, as we get more details, you may want to consider whether you want to be included in the registry.

Neurologist Awareness

This month, Dr. Jose Biller of Loyola University Chicago Stritch School of Medicine joined our scientific advisory board. Dr. Biller is a nationally known neurologist with a specialty in cerebrovascular illnesses.



From his faculty page at the Stritch Medical School:

Dr. Biller is a graduate of the School of Medicine, University of Republic, Montevideo, Uruguay. He was a resident in Neurology at Loyola University Chicago Stritch School of Medicine and completed a fellowship at the Bowman Gray School of Medicine at Wake Forest University, Winston-Salem, N.C. Just prior to joining Loyola, Biller was professor and chairman of Neurology at Indiana University School of Medicine. Prior to that, he served as director of the Stroke Program and the Acute Stroke Care Unit at Northwestern Memorial Hospital, Chicago.

Dr. Biller has published more than 200 peer-reviewed journal articles, contributed chapters and book chapters to more than 120 publications, and given more than 360 lectures and presentations. He currently is vice chair, Committee on Subspecialty Certification in Vascular Neurology, American Board of Psychiatry and Neurology (ABPN). He served as president of the ABPN in 2001 and was its director from 1994 to 2001. He currently serves on the editorial board for several publications including *Stroke*, *CNS Drugs*, *Neurology Bulletin*, *Neurological Research*, and since 2002, is the Editor of *Journal of Stroke and Cerebrovascular Diseases* as well as *Seminars in Cerebrovascular Diseases and Stroke*.

Dr. Biller has suggested that we approach our desire to increase neurologist awareness in several ways. His first suggestion was that we host regional medical conferences for neurologists so that they might be presented with information by the leaders in the field. Putting together such conferences would be a major undertaking for us – we are looking toward Fall, 2005 as a target for a first conference. We are looking forward to the challenge of making this a reality.

Secondly, Dr. Biller suggested that a review article about cavernous malformations in a major neurology journal would help education efforts. He and Dr. Awad will be working on such an article. We are very grateful for the support and work Dr. Biller is willing to give to us.

radiosurgery

By Jack Hoch

Radiosurgery, or non-invasive, radiation based treatment, is a compelling option for those suffering from diseases of the brain and body to which conventional surgical access is dangerous or impossible. Radiosurgery is not a panacea, but it does have practical applications in specific circumstances.

What is Stereotactic Radiosurgery?

Radiosurgery is the application of a high dose of radiation to a specific portion of the body. "Stereotactic" radiosurgery is the use of a three dimensional map (coordinate system) to deliver a predetermined amount of radiation to a precise location in the brain. Normally, it is delivered using a single dose session on an outpatient basis.

According to IRSA (<http://www.irsa.org/radiosurgery.html>) there are three basic types of radiosurgery:

- Particle beam (proton)
- Cobalt60 based (photon)
- Linear accelerator based

Photon-based radiosurgery is commonly known as "Gamma Knife", as the Gamma Knife machine is the most well-known and has been in use for over 30 years, treating nearly 100,000 people over this time period.

Benefits and Drawbacks

Each individual's case requires special attention, but generally speaking the following are the most important benefits and drawbacks of radiosurgery:

Good:

- Applied in a single session
- Used on an outpatient basis; no lengthy or costly hospital stay
- Minimal "recovery" time compared with conventional surgery
- Documented success for specific applications
- Non-invasive; practically eliminates potential for serious infection
- Any acute side effects are normally transient

Bad:

- Side effects are not uncommon and include:
 - o Swelling (edema) – can cause transient neurological symptoms (deficits); sometimes steroid meds are prescribed to combat swelling; worst cases may require placement of a shunt to relieve fluid build-up.
 - o Necrosis – death of healthy tissue. If any healthy tissue is involved in the irradiated area, deleterious effects on good tissue can result.
- Delayed onset of radiation-induced complications – it may take as long as six to nine months before serious complications result. These complications are, more often than not, permanent.

Radiosurgery and Vascular Malformations

Radiosurgery has acquired an excellent reputation as the procedure of choice in combating arteriovenous malformations (AVM). Used in conjunction with embolization, dangerous AVMs can be completely eliminated; however, the composition and structure of AVMs are quite different from that of other vascular lesions. The benefits of radiosurgery do not necessarily transfer to other malformations such as cavernous malformations (CCMs), venous malformations, or capillary telangiectasias.

The Controversy of Radiosurgery vs. Microsurgery for CCMs

If there is one "lightning rod" topic addressed by the vascular neurosurgery community, radiosurgery vs. CCMs is that topic. While both CCMs and radiosurgery have been around for

decades, CCMs are, at best, poorly understood. CCM natural history has only been documented in depth and number within the last 10 years, thanks mostly to the advent of MRI. Medical science has not yet determined the root cause and predictive hemorrhaging behavior of CCMs. Developing a "cure" or a process to deal with an entity of unknown origin and pattern of behavior is problematic at best.

The resultant schism divides most of the neurosurgical community into two camps (assuming we're dealing with an aggressive lesion requiring some type of action, not "expectant management"): those who advocate conventional surgery for CCM removal (the majority), and those who think radiosurgery has a role in the reduction of CCM hemorrhagic potential. There are very few neurosurgeons who take the middle ground by equally favoring both solutions to this issue.

Why the great divide? There has not yet been a 100% conclusive study that radiosurgery is an effective solution. While a few retrospective studies have been done, to date, not one randomized prospective study has been completed. Irrefutable evidence does not exist showing that radiosurgery reduces or eliminates future hemorrhagic events versus the natural history of the disease. Also, there have been cases where longer term results from radiosurgery have been less than ideal, causing patients to seek conventional surgical resection to alleviate persistent symptoms. In many cases, the radiation was a complicating factor, reducing the effectiveness of the follow-on conventional surgery.

Some radiosurgery studies, Gamma Knife studies in particular, indicate that there is a reduction in longer term hemorrhage rate after the procedure [Kondziolka], [Hasegawa], while other studies also show higher complication rates [Steinberg]. Even with Gamma Knife, some complication rates were unacceptably high [Pollock et al]. Pollock and Karlsson both agree that,

"whatever limited hemorrhage protection is provided by radiosurgery is not sufficient to accept the high risk of delayed radiation-related complications associated with radiosurgery of CCMs." [Pollock]

Most importantly, radiosurgery does not remove or obliterate the lesion [Gerwitz et al]. Changes in lesion size cannot be indexed conclusively to radiosurgery. In many cases, lesions are dynamic, and it is impossible to attribute change in size or volume to an external procedure.

One proposed hypothesis attempts to explain why radiosurgery surgery may not be suited for CCMs:

Avoiding the haemosiderin fringe is difficult in practice because of the intimate relationship of the ring to the periphery of the cavernoma and uncertainty in accurately determining the lesion's edge... The haemosiderin fringe surrounding the cavernous malformation is therefore likely to be generously dosed during radiosurgery. [St. George]

In other words, the properties of the "haemosiderin" (aged blood products; "hemosiderin is the American spelling) ring make it difficult to ascertain the exact boundary of where the lesion ends and healthy, albeit hemosiderin stained, brain tissue begins. This is in spite of the fact that:

Most authors agree, without venturing a scientific aetiological basis for their observations, that there is a higher incidence of sub-acute radiation reactions following radiosurgery for cavernous angiomas as compared to AVM or other targets, notwithstanding lower recommended marginal doses than employed for AVM targets [St. George].

This report stipulates that despite using lower dosage rates in CCM vs. AVM cases, more radiation-induced complications were seen with the CCM cases.

Finally, neurosurgeons at the Barrow Institute commented on the efficacy of radiosurgery radiosurgery in the treatment of CCMs:

“First, radiation treatment of angiographically occult vascular malformations does not “cure” these lesions. Hence, even after treatment, there is a continued risk of hemorrhage. Radiographic documentation of a lesion eliminated after radiosurgery has yet to be published. Second, the risk of radiation injury is significant and must be considered and compared with the outcomes of conventional surgical treatment of these lesions. Third, patients who had received radiation therapy before surgical resection had the worst postoperative course.” [Gerwitz].

On the other hand, conventional surgery in most cases can remove 100% of the lesion. Dramatic improvements in microsurgical techniques and experience now allow successful resection of malformations, which would not have been touched five years ago. There is at least one neurosurgeon who has changed positions in this debate and has stopped performing radiosurgery as the primary means to treat deeply seated cavernous malformations [Coffey].

The downside is that conventional surgery brings with it a longer and non-trivial patient recovery time. In some cases if the lesion is not completely resected, it can and does regenerate. Of course, there are instances where the lesion is both aggressive and surgically inaccessible without undue risk of mortality. It is this subset of patients, when all other alternatives have been considered and discarded, to which Gamma Knife may be most suited.

Until a definitive, randomized, multi-centered prospective study is completed, radiosurgery as a treatment modality for CCMs will continue to polarize the neurosurgical community.

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Latest Research

Frequency of Familial Forms of CCM

Two studies out of McGill University in Montreal looked at the frequency of specific mutations. In the first, researchers screened 35 cases which appeared to be the sporadic, rather than the familial form of the illness. They found that of those who had multiple cavernous malformations, 29% did have the familial KRIT1 mutation. No one who had a solitary malformation had the KRIT1 mutation. They conclude that "sporadic cases with multiple malformations warrant the same approach as individuals who have a familial history of CCM."ⁱ

In the second study, the same researchers looked at a large number of families with the hereditary form of the illness. They determined that 13% of the families had the CCM2 mutationⁱⁱ.

Genetic mutation affects the development of the arterial system

A mouse study coming out of Dr. Doug Marchuk's CCM lab at Duke studied the development of cavernous malformations in embryonic mice with the Ccm1 mutation (the mouse version of the CCM1 mutation in humans) in both sets of genes (homozygous). Mice that do not have at least one functioning Ccm1 gene die very early in gestation. It appears that the Ccm1 mutation causes the formation of cavernous malformations by affecting the development of the arterial system. The Ccm1 mutation impedes the full expression of other genes that are essential for artery formation (Efnb-1 and Notch)ⁱⁱⁱ.

KRIT1 mutation affects a variety of cells

Dr. Gunel's lab at Yale has been performing in-depth studies on where the KRIT1 protein is expressed and how it functions. It is a mutation in the KRIT1 gene that causes the CCM1 form of familial cavernous malformation. His lab's latest publication concludes that KRIT1 plays a role in more than just endothelial cells. KRIT1 was found "in cells and structures integral to the cerebral angiogenesis and formation of the blood brain barrier. These cells include endothelial cells and astrocytic foot processes, as well as pyramidal neurons in the cerebral cortex."^{iv}

Many genes may be involved in CCM

Dr. Judy Gault in Dr. Awad's lab at the University of Colorado published a review article which examined the pathobiology of cerebral cavernous malformations, hereditary hemorrhagic telangiectasia, and AVM's.^v Much of this article is quite technical. It explores the biology of vasculogenesis and angiogenesis and describes the recent understanding of the expression of structural proteins in vascular malformations. However, there are a number of interesting findings from other studies that we have not yet included in our Latest Research section. First is the original study which identified the existence of the CCM2 and CCM3 genes. This study indicates that the three genes which can cause the familial form of CCM have different rates of "penetrance." Penetrance is defined as what percentage of people with the mutation actually exhibit symptoms. This study lists the possible penetrance of CCM1, CCM2, and CCM3 as being 88%, 100%, and 63% respectively.^{vi}

A study out of Dr. Awad's lab last year determined that many hundreds of genes are altered in cavernous malformation tissue when compared with normal vascular tissue. This leads to a very important conclusion: many genes may play a role in CCM. From the article: "In summary, genes involved in the growth, integrity, and maintenance of blood vessels and immune response may be important disease modifiers in CCMs and AVMs. These modifiers may affect the severity of the disease, including lesion size and age at clinical presentation, or may be associated with specific clinical manifestations, including hemorrhage or epilepsy." They encourage

labs to examine all of the possible genes systematically to see what role each might play.

Imaging – Using Contrast Dyes during MRI

Contrast dyes are used during MRI to differentiate vascular malformations. Contrast enhancement is not usually seen with cavernous malformations. In a case study from the Technical University in Aachen, Germany, radiologists noted that by waiting one hour after the contrast dye has been injected before performing the MRI they were able to see slow, but intense, contrast enhancement in a cavernous malformation. They suggested that this approach might be useful in diagnosing cavernous malformations in atypical cases.^{vii}

ⁱ [Verlaan DJ, Laurent SB, Sure U, Bertalanffy H, Andermann E, Andermann F, Rouleau GA, Siegel AM.](#) CCM1 mutation screen of sporadic cases with cerebral cavernous malformations. *Neurology*. 2004 Apr 13;62(7):1213-5.

ⁱⁱ [Verlaan DJ, Laurent SB, Rochefort DL, Liquori CL, Marchuk DA, Siegel AM, Rouleau GA.](#) CCM2 mutations account for 13% of cases in a large collection of kindreds with hereditary cavernous malformations. *Ann Neurol*. 2004 May;55(5):757-8.

ⁱⁱⁱ [Whitehead KJ, Plummer NW, Adams JA, Marchuk DA, Li DY.](#) Ccm1 is required for arterial morphogenesis: implications for the etiology of human cavernous malformations. *Development*. 2004 Mar;131(6):1437-48.

^{iv} [Guzeloglu-Kayisli O, Amankulor NM, Voorhees J, Luleci G, Lifton RP, Gunel M.](#) KRIT1/cerebral cavernous malformation 1 protein localizes to vascular endothelium, astrocytes, and pyramidal cells of the adult human cerebral cortex. *Neurosurgery*. 2004 Apr;54(4):943-9; discussion 949.

^v [Gault J, Sarin H, Awadallah NA.](#) Pathobiology of human cerebrovascular malformations: basic mechanisms and clinical relevance. *Neurosurgery*. 2004 Jul;55(1):1-17.

^{vi} [Craig HD, Gunel M, Cepeda O, Johnson EW, Ptacek L, Steinberg GK, Ogilvy CS, Berg MJ, Crawford SC, Scott RM, Steichen-Gersdorf E, Sabroe R, Kennedy CT, Mettler G, Beis MJ, Fryer A, Awad IA, Lifton RP.](#) Multilocus linkage identifies two new loci for a mendelian form of stroke, cerebral cavernous malformation, at 7p15-13 and 3q25.2-27. *Hum Mol Genet*. 1998 Nov;7(12):1851-8.

^{vii} [Thiex R, Kruger R, Friese S, Gronewaller E, Kuker W.](#) Giant cavernoma of the brain stem: value of delayed MR imaging after contrast injection. *Eur Radiol*. 2003 Dec;13 Suppl 4:L219-25.