Angioma Alliance Newsletter

March, 2003

Editor: Connie Lee

Meet Our New Board Members

In January, I sent out a message asking for volunteers to join our Board of Directors. I am happy to report that three people have agreed to volunteer their time and talents. The new members (listed alphabetically) are:

Kristen Dehn
Kristen was diagnosed with multiple cavernous angiomas in March, 2002 and has undergone brain surgery to remove one angioma. Kristen has a number of affected family members, and she is dedicated to helping children who carry the diagnosis. Currently, she is working toward a masters degree in special education. Kristen will be helping Angioma Alliance to shape our outreach and support programs. Her experience and sensitivity are essential ingredients for making sure that we truly are addressing the needs of those affected by cavernous angioma.

Jack Hoch
Jack is a 41-year-old husband and father of two active boys, ages 4 1/2 and 21 months. He was diagnosed with a hemorrhaging cavernous angioma of the medulla oblongata (lower portion of the brainstem) in September, 2001. Jack has the sporadic form of the illness. Within two scary months, his neurological symptoms had resolved to the point where he could resume a mostly normal life. Jack can drive, work full-time at his job as webmaster of the AAA Foundation for Traffic Safety, and even play an occasional game of tennis, which is a tad more difficult now that he sees two tennis balls coming at him! The dark cloud that hangs over him, however, is that the cavernous angioma is not (currently) surgically accessible. He says that he remains adamant that he won't let this thing beat him.

To this end, Jack has dedicated himself to staying on the leading edge of cavernous malformation research. He has gained an understanding of medical terminology and of many of the issues involved in diagnosing, managing, and treating cavernous angiomas.

Jack has joined the Angioma Alliance Board of Directors to assist in interpreting medical journal research reports. His first article, on brainstem cavernous angiomas, appears below. Although Jack stayed at a Holiday Inn Express last night, this article, along with all other medical information articles on the Angioma Alliance site, has been reviewed by Dr. Awad.

Krista Zug
In 1993, Krista was diagnosed with multiple cavernous angiomas. She has chronic headaches and has had a mild seizure disorder most of her life which may or may not be attributable to her illness. Like Kristen, Krista has numerous family members affected by the illness. Krista works as a speech recognition specialist. This means that she helps people who are not able to use computer keyboards because of physical limitations to use their voice to control their computer. As a result of this work, Krista has developed a familiarity with a broad range of resources for the disabled. She will be helping us to develop a webpage specifically for those who are experiencing disabilities as a result of their illness. Krista will be helping in a number of other ways. She has already been active in the effort to bring Angioma Alliance to the awareness of others with the illness through links with other organizations. She will be assisting us in obtaining corporate grants to support our work and in finding other ways to keep Angioma Alliance financially sound. As a longer range project, Krista will be working toward developing a support program for those without local support/family as they go through diagnosis, surgery, and recuperation.

Please join me in welcoming these three talented people to the Board!

Update of Latest Research Results - March, 2003

There have been a small number of developments since our original publication of Latest Research Results in September, 2002. Topics which have received attention include surgical techniques, the expression of CCM in other areas of the body, venous angioma, and radiation.

Surgery
Studies out of Harvard[1] and Tokyo[2] describe apparently unique approaches for accessing two particularly hard-to-reach areas of the brain stem, the posterolateral mesencephalon and the ventrolateral medulla. Other studies explore the use of imaging techniques during surgery. In Aachen, Germany, surgeons have successfully combined diffusion-weighted MRI with functional MRI to visualize the large nerve fiber tracts which carry information to and from functionally important areas of the brain.[3] Another German study continued the exploration of the use of functional MRI and neuronavigation to reduce the chance of causing damage to brain tissue. Functional MRI and neuronavigation can help the surgeon to remove more or all of a lesion with less risk to the functioning of the patient.[4] A third German study compared the outcomes of surgeries in which either frame-based or frameless stereotaxy had been used. They concluded that frameless stereotaxy provided more flexibility in approaches along the skull base and midline. Frame-based stereotaxy appeared to be more accurate for lesions less than 7 mm[5]. Finally, in Korea, surgeons explored the use of a fibrin glue injection to control bleeding during the removal of a CCM from the cavernous sinus.[6]

Expression of CCM in other areas of the body

Expression of the KRIT1 protein during development has been explored in two separate studies. In the first, a French research group demonstrated that the KRIT1 protein was expressed primarily in nervous system and epithelial tissue in both mice and people.[7] A second study confirmed that the KRIT1 gene is expressed more widely in development, including in bones, skin, tendons, and meninges in mice, and suggested that KRIT1 has a functional significance that is "not restricted to vascular endothelial cells".[8] Along similar lines, two studies out of Johns Hopkins have demonstrated that cavernous malformations may be found in tissue outside of the nervous system in those with familial cavernous malformations. One family with CCM was found to have family members with cavernous malformations in the vertebrae as well as on their skin.[9] A case illustration indicated that cherry angiomas on the skin may be associated with familial CCM.[10] Taken together, these studies indicate that familial CCM may not always be confined to the nervous system.

Venous Angioma

There was a recent article on the topic of venous angioma (venous malformation or venous anomaly). The case study implies that venous angiomas may be responsible for causing the development of some cavernous angiomas. They describe an example of a man who had one cavernous angioma and two venous angiomas. Eight years after his initial diagnosis, he was found to have developed a second cavernous angioma adjacent to the venous angiomas.[11] See Some Answers from Dr. Awad below to read more about venous angiomas.

Radiation

A published article out of Emory University reports the case of a 17-year-old who presented with a spinal cavernous malformation 13 years after receiving craniospinal radiation for the treatment of cancerous tumor. The authors urge close follow-up of children who receive spinal radiation treatments.[12]

Brainstem Cavernous Angiomas

By Jack Hoch

Brainstem cavernous angiomas have recently received a great deal of attention due to enhanced imaging techniques and the realization that even small hemorrhagic events can cause significant neurological deficits. While the majority (approx. 75%) of cavernous angiomas occur in the upper ("supratentorial") region of the brain, about 1 in 5 are located in the brainstem or in highly sensitive ("eloquent"), lower ("infratentorial ") areas of the brain.[13] The most common symptom for brainstem lesions is focal neurological deficit as opposed to seizure or headache for lesions located in surpratentorial regions.

Cavernous angiomas of the brainstem present particular problems to both the affected individual as well as the neurosurgeon. Tightly packed nuclei inhabit the narrow conduit of the brainstem. Any additional mass or introduction of fluid, such as blood products from a bleed, can compress or crush important nerve fibers.[14] In other words, the smallest of intrusions can result in significant, and potentially life-threatening, symptoms. The nerves that transverse the brainstem control basic, involuntary functions such as respiration, gag reflex, heartbeat regulation, body temperature, pain and heat sensation, and hiccupping as well as other voluntary functions including eye movement, swallowing, facial muscle control, walking, and speech. Both cranial and "long tract" (whole body) nerves can be affected. For the individual, a brainstem cavernous

angioma can manifest a disparate range of symptoms making diagnosis difficult. The neurosurgeon must worry about how to manage the case and whether the inherent risks of brainstem surgery are worth the potential beneficial rewards.

While the root cause of a cavernous angioma hemorrhage is not yet understood, there are some consensus guidelines relating specifically to brainstem cavernous angioma case management:

1. Watch and wait ("conservative" case management). This consists of routine, periodic MRIs to monitor the changes in the lesion. As long as the lesion appears stable and there are no additional symptoms or evidence of hemorrhage, this is usually the most prudent course of action.
2. Surgical removal ("resection") may be considered if at least one of the following is true[15]:
    - The lesion abuts the surface of the brainstem that abuts the pia mater, the outer covering of the brain. This type of lesion is called "exophytic".
    - Repeated hemorrhages result in progressively worse deficits
    - Acute hemorrhage is external to the "capsule" of the lesion. In other words, blood from a hemorrhage is entering brain tissue surrounding the cavernous angioma.
    - The cavernous angioma has grown to a point where it is pressing upon surrounding brain tissue in a way that causes a visible compression of the surrounding tissue.
3. One study measured re-hemorrhaging rates as high as 30% per person per year.[16] Other studies show varying rates of re-bleeding.
4. Venous anomalies are frequently associated with cavernous angiomas of the brainstem. One study found that all 86 patients met this criterion. It is important to note that any associated venous anomalies should remain undisturbed during surgical resection of cavernous angiomas, as they provide functional drainage.[17] Elimination of these anomalies can result in infarction and death.
5. Surgical approaches involving cutting through the floor of the 4th ventricle should be avoided at all costs.[18] This does not preclude surgery as an option should the cavernous angioma abut the 4th ventricle floor; rather, the neurosurgeon must steer clear of approaching the lesion through the floor of this ventricle.
6. Stereotactic radiosurgery ("gamma knife") is generally not an accepted method of treatment for brainstem cavernous angiomas.[19] Relatively high morbidity rates can result, although one study noted reduced hemorrhage rates after radiosurgery.[20] Unlike radiotherapy for arteriovenous malformations (AVMs), stereotactic radiosurgery does not result in obliteration of the angioma.[21] At a minimum, radiosurgery treatment for brainstem cavernous angioma is controversial.
7. Given the advancement in minimally invasive surgical techniques, more and more neurosurgeons are becoming comfortable with surgical removal of cavernous angiomas from the brainstem; however, the potential for significant functional deficits from surgical complications is still significant. This risk must not be taken lightly. The decision to proceed with surgery should be weighed very carefully and implemented only on a case-by-case basis. Assuming one

meets the criteria established in part 2 above, one may wish to ask some additional lifestyle questions to help arrive at a decision:

- Can I still drive?
- Can I work?
- Can I take care of the family?
- Can I... (whatever else is important in your life)?
- Are the symptoms becoming progressively worse?
- Am I in decent physical condition to survive the rigors of brain surgery?
- Am I young enough such that the odds of having another hemorrhage are greater than if I were much older?
- Do I have enough of a support network to help me transcend the potentially arduous recovery process?

Finally, here is a word about diagnostics and imaging. Smaller cavernous angiomas are somewhat difficult to detect. Insist that one of your MRI sequences consists of "gradient-echo" (as opposed to spin-echo or proton beam) imaging. Gradient-echo MRI is most efficient at detecting small, or even punctate (point sized), cavernous angiomas.[22] Even though a spin-echo MRI may have detected a lesion, it's always prudent to ensure that there are not additional, smaller lesions which might become a problem later in life.

Some answers from Dr. Awad

We asked Dr. Issam Awad, chair of our Scientific Advisory Board, a few of the common questions that have been surfacing on our Community Forum and List Server.

On Venous Angiomas:

Q**: Do venous angiomas cause hemorrhage?**
A: Venous angiomas rarely hemorrhage. In all cases in which a pathology report was available, an associated cavernous angioma was the cause of a bleed.

Q: Should venous angiomas ever be removed surgically?
A: No, because they provide functional drainage.

Q: Can venous angiomas be a precursor of cavernous angioma development? In other words, do people who have had only a venous angioma sometimes develop a new cavernous angioma near the venous angioma?
A: An expanding number of case observations point in that direction.

On Activity Restrictions:

Should you restrict your physical activities if you are diagnosed with a cavernous angioma?
There is no scientific reason to restrict physical activity. There is some evidence that pressure within a cavernous angioma increases with Val Salva's maneuvers, interpreted as extremely heavy exertion such as with bench pressing. However, there is no evidence that this increase in pressure has led to bleeding.

Should people with cavernous angiomas, particularly those in the brainstem and spinal cord, restrict themselves from flying?
There is no scientific evidence that flying should be restricted, and there are no published cases where this has harmed anyone.

On Pregnancy Risks:

Can you explain in more detail the risks associated with pregnancy for those who have a cavernous angioma?
The evidence that pregnancy increases risk of cavernous angioma hemorrhage is controversial. Even if there were some increased risk, there is much experience with patients who complete pregnancies safely. These patients should have their cavernous angiomas judiciously monitored, especially if any headaches or symptoms arise. I've never had to intervene in dozens of cases with a known cavernous angioma carried through pregnancy. Other cases that present with hemorrhage during pregnancy may or may not have been caused to bleed by pregnancy. My advice for those with a known cavernous angioma is to consider surgery to remove symptomatic angiomas before a planned pregnancy if this is possible. Other angiomas should be followed under the care of a physician familiar with these lesions. Often obstetricians choose elective caesarian delivery or induced assisted labor, but there is no evidence that this is necessary if a lesion has not changed during pregnancy.

How Do I Find a Surgeon?

Much of the mail that is received at info@angiomaalliance.org comes from people who need help finding a neurosurgeon. In researching doctors, I've found a number of very useful links.

In the US:

Step 1: Check out the NEUROSURGERY://ON-CALL® Online Directory. Type in a city and state, then check the box next to "Cerebrovascular" under the Section Membership header. This will give you the names, addresses and phone numbers of all cerebrovascular surgeons practicing in that city. If no cerebrovascular surgeons are listed, you will have to try another city.

If you have a child with cavernous angioma, you may want to check the box next to "Pediatric" under the Section Membership heading. Unfortunately, there are very few neurosurgeons in the US who are members of both sections. You can find them by checking both the "Cerebrovascular" and the "Pediatric" boxes.

Step 2: Now that you have a few names, you may be able to find out more about each doctor on the internet. If the doctor is associated with a university or medical school, go to the school's home page (you can usually find it easily using a search engine) and begin following links until you get to the Neurosurgery faculty page. Most medical schools list the specialties of each faculty member. If you see "vascular malformations" or some variant of "cavernous malformation" listed under specialty, the doctor should have familiarity with your condition. I also like to know where a doctor has received his or her training, but judging this requires more information about training institutions than most of us would have.

Step 3: Another way to get to know your doctor is to see what articles, if any, they have published in medical journals. The National Library of Medicine's PubMed service allows you to see article titles and their abstracts. When you reach the page, type in your doctor's name in the "Search PubMed for:" box. You will get the best results if you can use the following format:

For Dr. Angela Jane Smith,
Type in **Smith AJ**

If you don't know your doctor's middle initial, you can leave it off. You may get a list of many articles not written by your doctor, but you can usually narrow this down by looking for specific cerebrovascular terms in the titles. If you'd like to read the abstracts, that's great. But, it is enough simply to get a sense of where your doctor's interests lie by looking at key words, like "cavernous malformation" or "arteriovenous malformation", in titles. Don't despair if your doctor has not published recently or has not published in this area. Many hospital-affiliated doctors are too busy with their clinical practices to do much publishing. It gives you more information if your doctor has published, but it does not say anything about the competence of a doctor if he or she has not.

Internationally:

Step 1: You can access names of neurosurgeons in your country in a few ways. Try the NEUROSURGERY://ON-CALL® Online Directory by typing in your country name and checking the box next to "Cerebrovascular" under the Section Membership header. This will give you a small list of names, unless you are checking from Canada where the list would be longer. You will find additional names by checking the World Directory of Neurosurgeons. Unfortunately, this listing does not break out doctors by specialty. Finally, most countries have their own neurosurgical professional organizations. Some of these organizations have web sites with their own directories. You may be able to find the organization through a major search engine like Google.com using some combination of your country name, "neurosurgery", "professional", and "association".

Steps 2 and 3: Are the same as for those searching for US doctors above. Looking for a doctor's faculty listing and searching for publications on PubMed work just as well internationally. PubMed lists articles published in all major medical journals, not just those in the US.

Tidbits

Our Patient Education Brochure

Through email and regular mail, Angioma Alliance has notified about 800 cerebrovascular and pediatric neurosurgeons and 1200 genetics professionals about our organization. We have received orders for about 1000 copies of our brochure, mostly from university medical centers in the Mid-West and Canada. For many patients, this will be the only written information they receive about their illness.

GlaxoSmithKline Grant

Angioma Alliance is very pleased to announce that we have received a $1,000 grant from GlaxoSmithKline to support our outreach to those affected by cavernous angioma who may not have internet access. As a result of this grant, we will be able to broaden the scope of our patient education brochure distribution to a broader range of neurosurgeons and to neurologists.

Familial Cavernous Angioma Link

Eric Johnson, Ph.D., a member of our scientific advisory board and a neuro-geneticist at the Barrow Neurological Institute, has published a very informative summary of the genetics of familial cavernous angioma on the GeneReview website. The link is http://www.geneclinics.org/query?dz=ccm.

List Server Updates

The List Server is up and running. By signing up to be part of the list server, you become able to send an email to an entire group of people affected by cavernous

angioma at the same time. This allows for group discussions, the creation of one-on-one connections, and the building of a community. If you are having trouble signing up for or using the list server, please don't be shy about contacting me at info@angiomaalliance.org. I'd be happy to walk you through it.

Ebay Celebrity Clothing Auction!

We are trying to create a charity auction on Ebay to benefit Angioma Alliance. We've just started mass mailing celebrities, hoping to receive donations of autographed clothing. If we're successful, there will be an Ebay auction in May. If you know someone famous that you could contact or if you have an autographed item you'd be willing to donate, we would be extremely grateful for your help.

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