ANA/NJ Newsletter
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Chapter Meeting, Plainsboro
March 26, 2017

Our Spring meeting was held at the University Medical Center of Princeton at Plainsboro. Twenty-six people including five board members were present. Unfortunately, Dr. Patricia A. Graham, our scheduled speaker for the topic "Integrative Medicine Approaches for AN Patients," was unable to attend because of sudden illness. The meeting went forward nevertheless and developed successfully into an open and lively discussion about past and recent patient experiences with acoustic neuroma. We wish to extend our sincere thanks to staff of the Princeton Center for their special assistance in preparation for this meeting.

To summarize briefly: One Wait-and-Watch patient reported on how his 1.4 - 1.6 cm tumor was discovered 'incidentally' ten years ago. Two patients spoke about having retrosigmoid surgery: one has been confronted with continuing post-op headaches; the second (a 2-3.5cm cystic tumor) lost hearing and had brief balance problems. A patient with a 2.4cm tumor decided to have Gamma Knife radiosurgery. A patient with a small 1.4-1.8cm AN decided on Wait-and-Watch; whereas another patient with a small 1.4cm tumor decided on surgery because of acute symptoms. A patient with a rare case of bilateral ANs, who has kept us up-to-date on his Wait-and-Watch status, reported that he has been in touch with Jefferson Medical College in Philadelphia about possible hyperfractionated radiation treatment (multiple low dose sessions) for tumor growth control.

There were questions about remediation for tinnitus (see the Newsletter for Sept 2014 for active support groups in New Jersey) and CROS hearing aids (e.g., Widex, Phonak) for single-sided deafness (see the Newsletter for March 2013). Jane Huck is currently asking for information about hearing aids used by ANers for inclusion in the next issue of our Directory.

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Schwann Cells

During the half-century that has elapsed since the enunciation of the cell-theory by Schleiden and Schwann, in 1838-39, it has become ever more clearly apparent that the key to all ultimate biological problems must, in the last analysis, be sought in the cell. . . .

Edmund B.Wilson
The Cell in Development and Inheritance (1896)

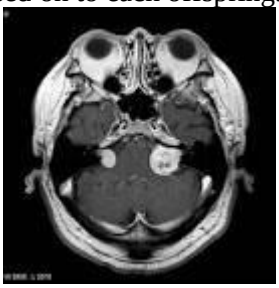
Schwann cells were first identified in 1838-39 by the German physiologist Theodore Schwann (1810-82) who, as noted in the above quotation, was also the co-founder with the botanist Matthias Schleiden of the critically important cell theory that all living things are composed of cells. His early classification of different cells in the human body marked the beginning of modern histology, the microscopic study of cells and tissues.

Most acoustic neuroma patients hear about Schwann cells for the first time when their tumor is diagnosed. They learn that their tumor originates (tumorigenesis) when Schwann cells misbehave. Normally, Schwann cells function beneficially to form an insulating myelin sheath on the vestibulocochlear (8th cranial) nerve to protect and speed along balance and sound information from the inner ear to the brain. At times, however, things go awry. A by chance ("out of the blue") mutation in the NF2 gene on chromosome 22 results in losses in the cell protein named *merlin*, and Schwann cells multiply uncontrolled to form a schwannoma. Serious efforts are currently underway to gain insights into the biological functioning of the tumor suppressor protein *merlin*.[1]

A Case of Bilateral ANs

For the great majority (ca. 95%) of acoustic neuroma patients, when Schwann cells misbehave, the consequence is a unilateral AN affecting the vestibulocochlear nerve in one ear. The AN is called "sporadic," meaning it's the result of a chance mutation. The tumor is benign and not hereditary. It can become 'troublesome', but most times it's readily treated successfully by modern medical techniques. And even if hearing should be lost in the affected ear, you still have a spare.

But suppose you find that you have an AN in each ear? Bilateral ANs! This is a much more worrisome condition. Bilateralism is considered to be the hallmark and main diagnostic criterion for neurofibromatosis type 2 (NF2), a genetic disorder that is heritable, progressive, very difficult to manage, and has a 1 in 2 chance of being passed on to each offspring.



(MRI of Bilateral ANs)

[1] See, for example, "Merlin: Not Your Average Wizard. How NF2 Research is Helping Discover Drug Therapies for Acoustic Neuroma," by Dr. Kristina Fernandez-Valle (Univ of Central Florida), ANA Support Group Meeting Video Library, November 12, 2016, at www.ANAUSA.org.

This is the condition that Jeff Miller spoke about at our March 26 meeting in Plainsboro. Jeff is Wait-and-Watch for bilateral ANs: 1.7cm on the left and 0.4cm on the right when reported for our July 2016 Directory. His condition is currently being monitored by Dr. Thomas Willcox (ENT-otolaryngologist) at the Thomas Jefferson University Hospital in Philadelphia. He has had genetic testing for NF2 at the University of Pennsylvania Hospital. Of course, Jeff has probed the Internet for information about his condition.

Jeff's case is unusual because NF2 has yet to be determined definitely. He has bilateral ANs, but no evidence of the additional brain or spinal cord tumors that are common to NF2 patients. His genetic testing proved to be negative for NF2. He has no family history of NF2. Also, persons with NF2 usually develop ANs on the vestibulocochlear nerve in their teens or early adulthood, whereas Jeff is 53 years old. He has learned that researchers at the University of Manchester, UK, recently used a database of 1,200 NF2 patients to discover evidence that about 25% of the bilateral ANs in individuals over 50 years of age were not NF2 related at all, but simply by chance "sporadic" ANs.[2] This was an encouraging finding. Having two "sporadic" ANs to deal with would still be problematic, but at least there would be no risk of transmitting NF2 to offspring.

It's quite possible, however, that Jeff has a condition called "mosaic NF2," a sometimes milder form of NF2 experienced by individuals who are first in their family to be affected. Only about 50% of people with NF2 inherit the disease; the other 50% of cases result from a new by chance genetic mutation. Some of these new mutations are known to result in milder symptoms and progression. Dr. Katherine Nathanson at the University of Pennsylvania called this condition to Jeff's attention as a likely reason for his negative test results.[3]

Jeff recommends that one of the most readable descriptions of "mosaic NF2" to be found on the Internet is the 6-page fact sheet prepared by staff and medical advisors of The Neuro Foundation, a charity organization for neurofibromatosis patients with offices in SW London, UK.[4] The following quotes in italics are key statements excerpted from this fact sheet:

When a new diagnosis of NF2 is made, where that person is the first in the family to be affected, and where they have tumors on both hearing nerves, then about 30% of this group of people will have mosaic NF2.

[*Mosaic NF2*] *is a term used to describe a situation where the genetic misprint that causes NF2 is present in some rather than all of the body's cells. . .*

In most people, the genes in every cell will contain the same information, whether they are blood cells, skin cells or cells in other tissues. . . However, some people will have a mixture of cells in their body. Some cells will contain the correct genetic information. Other cells will have a change in that genetic information. Someone with mosaic NF2 will have a mixture of cells. [Only some cells] will have the gene change that causes NF2. . .

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[2] D.G.Evans et al, "Bilateral Vestibular Schwannomas in Older Patients: NF2 or Chance?" *Journal of Medical Genetics*, 52, Issue 6 (2015).

[3] See also, for example, "Diagnosing Neurofibromatosis Type 2, Genetic Testing," NYU Langone Medical Center, www.nyulangone.org.

[4] "Information About Mosaic Neurofibromatosis Type 2," by Rosemary Ashton & others, The Neuro Foundation (January 2012), online at www.nfauk.org. (Note: "The Neuro Foundation cannot accept liability for any errors or omissions or for information becoming out of date.")

In someone with mosaic NF2, the result of a blood test will usually be "normal" because the blood cells do not have sufficient quantity of the NF2 gene change to detect it. . . The final stage of the diagnosis is to look for the gene change in the actual NF2 tumor itself. If a tumor is removed during surgery. . .the cells that form the tumor will definitely have the gene change.

In people with no family history of NF2, where NF2 has occurred by chance, about 30% of people will not have the NF2 misprint in all the cells of their body. A person who has a diagnosis of mosaic NF2 therefore tends to have a milder form of NF2.

It will be asked: Can mosaic NF2 be passed on (inherited)? For patients like Jeff who have some signs of NF2, but insufficient to confirm a diagnosis, the question is important. The fact sheet states:

If a parent has mosaic NF2, the chance of passing on NF2 to a child is less [than if a parent has NF2 in all their cells]. Nevertheless, if a child inherits NF2 from a parent who has a mosaic form of the condition, they will inevitably have the NF2 misprint in all their cells and therefore will have more NF2 problems compared to their parents.

Jeff has had periodic MRI scans to check for any growth in the size of his ANs. The tumor on the right side has remained steady at about 0.4 cm. The tumor on the left side, however, has shown slow growth since the first scan in 2015. The scan record for this tumor is as follows:

Left Side MRI Scans

Jan	2015	1.5 x 1.7 x 2.4 cm
Oct	2016	1.8 x 1.9 x 2.5 cm
Apr	2017	2.1 x 2.2 x 2.7 cm

The record shows slow growth, although much of this can be attributed to a cystic component of the tumor, and there has been no indication of any change in hearing. Following the April 2017 scan, therefore, Dr.Willcox decided to continue Wait-and-Watch management of the bilateral ANs for an additional six months.

Jeff has met with Dr. Christopher Farrell at Jefferson University Hospital to discuss possible treatments for his ANs, if or when needed, and he thinks that he may opt for having fractionated stereotactic radiotherapy (FSRT) rather than surgery. For many years under Dr. David W. Andrews' guidance, the Jefferson University Hospital has pioneered FSRT for achieving a greater rate of hearing preservation for acoustic neuroma.[5] But thoughts about treatment are pretty much "on hold" for Jeff as of this writing. This is because he has also been undergoing repeated surgeries for an intransigent chondro-sarcoma pelvic tumor at the base of the spine. Early on he tried a round of high dose radiation. Then came the surgeries. But the tumor has not responded to any treatment, and the bad news in January 2017 was that the tumor had once again recurred. Jeff is now busy looking into the route of genetic testing and clinical trials for a drug that might give some relief.

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[5]For example: David W. Andrews, Thomas O. Willcox, et al, "Toward Dose Optimization for Fractionated Stereotactic Radiotherapy for Acoustic Neuromas: Comparison of Two Dose Cohorts," in *Internat Jour Radiation Oncology Biol Phys*, 74, No.2 (2009). Patients in this study were treated with a dedicated stereotactic linear accelerator (LINAC), the Varian 600SR Clinac 6-MV. The fractions were 1.8 Gy, delivered daily 5d/wk for 4-6 weeks for a cumulative dose of either 50.4 Gy or 46.8 Gy.

"Synodos for NF2"

Members of the ANA support group in Sarasota, FL, were fortunate to have professor Kristina Fernandez-Valle, PhD, as their speaker to describe how neurofibromatosis type 2 (NF2) research is helping discover new drug therapies for acoustic neuroma (see above footnote for "Merlin: Not Your Average Wizard"). She is a dedicated researcher at the Burnett School of Biomedical Sciences, University of Central Florida, and a member of 'Synodos,' a unique consortium of key scientists organized in 2014 by the Children's Tumor Foundation in New York City with the ambitious goal of solving the problem of NF2.[6]

The name Synodos comes from the Greek terms meaning "to work together on the same path." This is the uniqueness of the consortium, that it "brings together a multidisciplinary team of scientists from twelve world-class labs at academic and medical centers of excellence, who have pledged to work closely together – sharing information, datasets, results and more – at every step in research development, with the goal of speeding up the drug discovery process." Collaboration and cooperation among researchers is emphasized, rather than competition and data hoarding.

In addition to the University of Central Florida, the labs working together are from Ohio State, Johns Hopkins, Massachusetts General (6 labs), Indiana, North Carolina and the Fritz Lipmann Institute (Jena, Germany).

"Key to this partnership is 'Sage Bio-networks,' a research institute that will 1) ensure data and knowledge are quickly disseminated throughout the consortia membership as it is produced, and 2) create an online, publicly-accessible record of the research performed by the consortia, allowing others to freely use the generated data for new purposes."

Who Invented MRI?

It is in the nature of the Nobel Prize that there will always be a number of candidates who obviously deserve to be rewarded but never get the accolade.

Ulf Lagerkvist (1926-2010)
Swedish Academy of Sciences

Paul Lauterbur Raymond Damadian Peter Mansfield

Ulf Lagerkvist's observation regarding the Nobel Prize pretty much sums up what happened in 2003 when the awards in Physiology and Medicine were decided. The two awardees, honored "for their discoveries in magnetic resonance imaging," were the American chemist Paul C. Lauterbur (1929-2007) and the recently deceased British physicist Sir Peter Mansfield (1933-2017).[7] A third very deserving candidate, Raymond V. Damadian (b.1936), the American physician-scientist-entrepreneur who in 1977

[6] For 'What is Synodos?' see Children's Tumor Foundation, www.ctf.org, and "CTF Announces Historic New Initiative in Neurofibromatosis Research" (March 10, 2014), www.globenewswire.com.

[7] Matt Schudel, "Peter Mansfield, 83, Helped Develop MRI," *The Star Ledger* (February 13, 2017).

built the first crude MRI scanner (now in the Smithsonian Institution), was denied any share in the Prize, even though three individuals could have been be named. Damadian protested vigorously that he was the true inventor of MRI; that his scientific discoveries were seminal for the idea of applying magnetic resonance to medical imaging. Two key documents supported his candidacy: (1) his March 19, 1971 article in the journal *Science* (vol.171), "Tumor Detection by Nuclear Magnetic Resonance," to show that he was the first to propose using magnetic resonance technology to scan the human body for early signs of malignancy; and (2) his 1974 patent papers for "Apparatus and Method for Detecting Cancer in Tissue," the first patent in the field of MRI scanners.[8] As Damadian said in 2004 in reference to these documents: "I made the original contribution and made the first patent. If people want to reconsider history apart from the facts, there's not much that I can do about that."[9]

Damadian complained that Lauterbur and Mansfield had contributed to MRI mainly by their refinements improving the quality of the machine's imaging. But for the awards in 2003, showing high scientific achievement in this area was deemed most important by the 50 members of the Nobel committee. In his awards presentation speech at the Karolinska Institute on December 10, 2003, Professor Hans Ringetz emphasized Lauterbur's discovery that variations in the magnetic field "made it possible to create two-dimensional images of structures" in the human body; and Mansfield was lauded for showing "how extremely rapid imaging could be achieved by very fast gradient variations (so-called echo-planar scanning)."[10]

Missing out on the Nobel in 2003 was a big disappointment for Damadian, but he had already garnered accolades by establishing the Fonar Corporation in Melville, New York, for the manufacture of MRI scanners. In 1982, Fonar patented technology which is the basis for all 'Open' MRIs. The company's unique 'Stand-Up' MRI was introduced in 1996. In 1988, President Ronald Reagan awarded Damadian the National Medal of Technology (jointly with Lauterbur); and in that same year he was inducted into the National Inventors Hall of Fame of the U.S. Patent Office.

Notices

● The joint NJ-NY mini-conference for acoustic neuroma has been scheduled for April 22, 2018, at the JKF Medical Center in Edison, NJ. Details to follow.

● The CaptionCall brochure announces: "Ask your hearing-care or healthcare provider to help you order a complimentary CaptionCall phone today!" The brochure explains that the Americans with Disabilities Act has established a fund to give eligible individuals with hearing loss access to captioned telephone service at no cost. The phone lets you read as well as hear your phone conversations. Installation and in-home training are free. An internet connection is needed. For further information, visit www.captioncall.com or phone 1-877-557-2227.

● A valuable public website for neurofibromatosis patients is *The Neurofibromatosis Network* (www.nfnetwork.org). The website provides "The

[8] See George Kauffman (Dept of Chemistry, California State University, Fresno), "Nobel Prize for MRI Imaging Denied to Raymond V. Damadian a Decade Ago," *The Chemical Educator*, 19 (2014); James Mattson & Merrill Simon, *The Pioneers of NMR and Magnetic Resonance in Medicine: The Story of MRI* (1996); "The Inventor of MR Scanning," at www.fonar.com/history.

[9] Quoted in *The New York Times* (March 23, 2004).

[10] See the official web site, www.nobelprize.org.

Network Edge," a trimonthly column by science writer Vanessa Merker reviewing research and clinical trials; a listing of important medical journal articles; notices of educational materials; links to NF chat groups; reports on cochlear implants; and audio-visual webinars, including "Hearing Preservation and NF2" by Dr. Derald Brackmann (House Clinic).

● Researchers Matthias A. Karajannis (NYU Langone) and R. Ferner (King's College London) have published "Neurofibromatosis-related Tumors: Emerging Biology and Therapies," *Current Opin Pediatrics*, 27 (Feb 2015). Dr. Karajannis spoke at our October 2014 Mini-Conference in Berkeley Heights.

● The Yale University Acoustic Neuroma Study investigating genetic risk factors for AN continues to collect questionnaires and patient DNA samples (Phase 1). But testing the DNA samples (Phase 2) is currently on hold due to insufficient funding. Go to "Research" at www.anausa.org for more information.

● Surgeons and engineers at Bern University Hospital in Switzerland have developed a "high-precision surgical robot for cochlear implantation." See www.meddeviceonline.com for "Instrument Flight to the Inner Ear" (March 17, 2017).

Chapter Meeting Fall 2017

"Acoustic Neuroma and Balance Issues"

Presented by

Dina Leyden, PT, Summit Medical Group

Dina Leyden is a specialist in physical therapy. She has expertise in vestibular rehabilitation, including positional vertigo and general balance and dizziness disorders. She has worked in a variety of health care settings, including hospitals, adult inpatient rehabilitation programs, home health, subacute care, and outpatient private practice.

Sunday, October 15, 2017

1– 4 pm

Summit Medical Group

Lawrence Pavilion, One Diamond Hill Road

Berkeley Heights, NJ

Refreshments Q&A Social Time

Directions

The most direct way to the Summit Medical Group facility in Berkeley Hts is via **Route 78.**

From **Route 78 East**, take Exit 43, Berkeley Hts/Watchung. Follow the exit road to the light at Valley Rd and turn left onto Valley Rd. Go to the first light and turn left onto Diamond Hill Rd. Follow Diamond Hill Rd to the light at Mountain Ave. Go left on Mountain Ave for a very short distance to the entrance to Summit Medical Group, on the left. You will see Lawrence Pavilion and parking straight ahead as you enter. Park to the right and look for the **ANA/NJ Meeting** sign.

From **Route 78 West**, take Exit 43, New Providence/Berkley Hts. Bear right onto Diamond Hill Rd. Follow the directions above for Summit Medical Group, Lawrence Pavilion.

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