

ANA/NJ Newsletter
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**Chapter Meeting, Berkeley Heights,
October 20, 2013**

Forty-two people attended the meeting. Dick Barker welcomed all and took the opportunity to call attention to the important Yale University Acoustic Neuroma Causation Study currently seeking participants (any person over the age of 20 with a diagnosis of acoustic neuroma). “The purpose of this study is to discover why some people develop acoustic neuroma while others do not.” For more information and also to begin participation, interested ANers can go to the national association website www.ANAUSA.org.

Our speaker was Dr. Jed Kwartler, Summit Medical Group. Dr. Kwartler had bravely volunteered to address the broad topic “What’s New for Acoustic Neuroma, 1993-2013.” For the meeting, he used slides to help present his thoughts on the subject. Some main ideas were:



- Symptoms for AN haven’t changed; hearing loss remains the most common symptom. But screening tests (e.g., ABR) are no longer used; patients with asymmetrical hearing loss now go right to MRI.
- The percentage of wait-and-watch patients has increased. Dr. Kwartler showed how this treatment option needed to be decided with reference to the known phases of tumor growth.
- Cases of pre-treatment facial paralysis declined, related to more and more ANs being discovered while still very small.
- Offering treatment options for acoustic neuroma has become a generally accepted practice.
- A big change is that surgery is now more ‘conservative.’ Total tumor removal is not always attempted. More attention is being given to the patient’s post-treatment quality of life.
- As facial nerve preservation improved, better useful hearing preservation became a new emphasis.. Dr.Kwartler advised that patients opting for radiation treatment need to inquire about short-term compared to long-term (follow-up) outcomes.
- Advanced hearing devices for SSD (e.g., Baha, Ponto, SoundBite, Cros) were introduced.
- Very exciting was the identification (1993) of the NF2 gene and its tumor suppressor protein called *Merlin*, which functions to prevent Schwann cell proliferation. Neurofibromatosis Type 2 research has been advanced. The research has involved testings of the drug *Avastin*, an angiogenesis inhibitor that shows promise for stopping acoustic neuroma growth by suppressing tumor blood vessel formation.

Notices

- Founded in 1992, the Central Brain Tumor Registry of the US (Carol Kruchko, President) is a non-profit corporation dedicated to reporting the incidence of all primary and central nervous system tumors in the US in order to facilitate research. In 2002, Public Law 107-206 mandated that, beginning in 2004, tumor data registries must include benign brain tumors such as acoustic neuroma. The data for 2012 showed acoustic neuromas to be 7-8% of all primary brain tumors. CBTRUS statistical reports are made available free at the website, www.cbtrus.org.
- ANAUSA has announced that Dr. Steven W. Cheung, a neurotologist at the University of California San Francisco, is seeking participants in an online survey (about 20 minutes to complete) to learn more about tinnitus and acoustic neuroma. Go to www.ANAUSA.org to participate. For questions, contact Dr. Cheung at scheung@ohns.ucsf.edu.
- For our Registry, Sandy Koreen (Long Branch) reported favorably on her 28-session proton beam treatment for a small AN (sessions completed December, 2012) at the new ProCure Proton Therapy Center in Somerset, NJ. She has recommended that ANA/NJ might provide information about proton beam therapy at a future meeting.
- Mass General Hospital in Boston is currently recruiting participants (18 yrs & older) for a clinical study of “Hearing Outcomes Using Fractionated Proton Radiation Therapy for Vestibular Schwannoma.” (est. completion date Sept 2014). The study is “to determine the effects of fractionated proton radiotherapy on long-term hearing preservation and controlling tumor growth.” For more information, go to www.clinicaltrials.gov and search ‘acoustic neuroma.’

Save the Date!

ANA/NJ Mini-Conference

October 26, 2014 9am – 4:30pm

Speakers and Location TBA

Thinking About the Causes of Acoustic Neuroma

In the classic movie *Casablanca*, when things go wrong, the suave police captain played by Claude Rains always orders his minions to “Round up the usual suspects.” It seems at times like we’re at a similar stage of investigation for the causes of acoustic neuroma. At least for environmental and lifestyle risk factors, we keep rounding up and questioning the same suspect trouble-makers, like cell phones, dental X-rays, CT exams, various screenings, noise pollution, smoking, ionizing radiation. It’s to be

hoped that the recently organized Yale University Acoustic Neuroma Causation Study led by Dr. Elizabeth Claus will be able finally to get the usual suspects sorted out and classified.

The investigation has moved forward to a higher stage for the category of genetic risk factors, where a major culprit is now known to be the NF2 tumor-suppressor gene located on chromosome 22. Mutations in this gene have been found to result in losses of the protein named *merlin* (a.k.a. *schwannomin*) which normally functions to prevent any proliferation of the Schwann cells that insulate neural nerves. Without *merlin*, the cells multiply uncontrolled to form tumors. Patients with the rare inherited condition called neurofibromatosis type 2 (NF2) have a genetic flaw in the NF2 gene and typically develop bilateral acoustic neuromas, usually in their teens or early adulthood.

The great majority of acoustic neuroma patients (95%) have unilateral ANs, which are not hereditary and occur most often between the ages of 40-60 years. These non-hereditary, unilateral ANs are called sporadic (meaning by chance) and appear to be acquired largely because of DNA-damaging environmental or lifestyle risk factors such as those listed above. Sporadic ANs may also be due in part to chance mistakes in DNA copying during the normal process of cell division. The NF2 gene on chromosome 22 is reputed to be especially vulnerable to chance mutation.

As might be expected, the NF2/*merlin* culprit has been interrogated extensively by numerous expert investigators since its identification in 1993.¹ These studies have confirmed that both NF2-associated and sporadic ANs are linked to the NF2 gene. This is not to say, however, that one culprit gene is the ultimate cause of all ANs. On the contrary, as the old saw puts it, “The plot thickens!” Continuing studies in genetic-molecular biology for NF2/*merlin* over the past two decades have rounded up a host of new suspects that appear to play important roles in the origin of acoustic neuromas. We should not be surprised. Dr. Francis Collins, the current director of NIH and a leading figure in molecular-genetic research, has aptly observed that our recently acquired ability to search the entire genome (“the entire set of genetic instructions found in a cell”) has led to the discovery of more and more risk factors for human diseases. In his book, *The Language of Life* (2010), Dr. Collins notes how “our understanding of how genes are regulated is undergoing dramatic revision, as the signals embedded in the DNA molecule and the proteins that bind them are rapidly being elucidated. The complexity of this network of regulatory information is truly mind-blowing, and has given rise to a whole new branch of biomedical research.”²

Take the case of sporadic ANs. Here, briefly stated, are some examples of the complexity identified by recent research. . . .

- Tissue studies of sporadic ANs by Drs. D.B.Welling (Ohio State Univ) and John M. Lasak (Kansas State Univ) have “suggested that there may be different mutational mechanisms involved in the tumorigenesis [tumor origin] of unilateral and bilateral schwannomas.” The researchers have identified “regulatory” DNA segments that may increase or decrease the merlin function, or reduce angiogenesis [tumor blood vessel development].³

- Researchers at Gutenberg University Medical Center (Mainz, Germany) have looked at twenty sporadic ANs to identify additional chromo- some regions that may harbor genes involved in tumorigenesis. Their 2011 report states that the NF2 gene is the only “established” causative event underlying schwannoma formation, and that “The most common changes were losses on chromosome 22. [But] additionally, losses were observed on chromosome 9p, indicating the possible participation of . . . a tumor suppressor gene in the genesis of VS [Vestibular Schwannoma, a.k.a. AN]. . . Importantly, high level amplifications have also been observed . . . suggesting the possible involvement of several oncogenes [mutated genes that push cells to divide] in the tumorigenesis of VS. Our data [in summary]

¹ A.Parsa et al, “Molecular Biology of Familial and Sporadic Vestibular Schwannomas: Implications for Novel Therapeutics,” *Journal of Neurosurgery*, 114 (Feb 2011). This is a review of the literature.

² *The Language of Life: DNA and the Revolution in Personalized Medicine* (Harper, 2010).

³ “The Genetics of Neurofibromatosis Type II and Acoustic Neuroma,” in *ANA Notes* (March 2003); *Human Genetics*, 98 (1996); *Otol.Neurotology*, 23 (2002).

suggest the involvement of various oncogenes and tumor suppressor genes might play a role in the genesis of vestibular schwannomas *apart from* the inactivation of the NF2 gene.”³ (Our italics)

- “A significant proportion of sporadic VSs [a.k.a. ANs] do not grow at all or grow very slowly, and some even decrease in size. At one center, among 40 sporadic VSs visualized with internal imaging, only 30% of the tumors showed evidence of growth over a 30-month follow-up period. Furthermore, the growth rate in 30% was ~1 mm/year. The clinical behavior of VS in NF2 is significantly different from that of sporadic VS. In patients with NF2, 75% of schwannomas show evidence of growth, with an average growth rate of 4.5 mm/year. Mechanisms other than and in addition to NF2 gene inactivation seem to be involved in the initiation and maintenance of VS growth. At present, there is no consensus on the important cellular factors that influence tumor growth in either sporadic VS or NF2.”⁴

- Studies from several laboratories suggest that the important NF2 protein *merlin* “may regulate cell growth in response to specific cues from the environment. . .” Results “suggest that *merlin* growth regulation occurs within the context of extracellular interactions provided by normal brain or nerve. The loss of *merlin* might lead to an impaired ability to respond to these environmental growth regulatory cues and culminate in increased cell growth, tumor formation, and tumor cell infiltration.”⁵

In 2007, with sporadic ANs (i.e., *most* ANs) in mind, Dr. Fred Barker (Mass General Hospital, Boston) concluded his article on “What Causes Acoustic Neuromas?” by saying, “we still don’t know exactly why *most* patients with acoustic neuromas have them, and I would strongly suspect that there’s plenty of interesting research . . . still ahead in the future.”⁶ It would appear that this appraisal still holds true today. For most ANs, we are still not able to explain exact connections between the molecular-genetic complexity (still under study) and environmental-lifestyle influences (still under study). Even for NF2-related ANs, where the known hereditary genetic flaw would seem to be enough of a trouble-maker, the new era in genetic-molecular biology has identified unexpected complexity. One important review of new findings for NF2, by Drs. Martin Rutledge and Guy Rouleau (McGill Univ), has stated: “It is likely that mutations in other, as yet unknown genes [apart from NF2] are necessary before a schwannoma. . . develops.”⁷

³ D. Koutsimpelas et al, “Analysis of Cytogenetic Aberrations in Sporadic Vestibular Schwannomas by Comparative Genomic Hybridization,” *Journal of Neuro-Oncology*, 103 (July 2011).

⁴ Parsa et al., note 1.

⁵ Ibid.

⁶ “What Causes Acoustic Neuromas?” *ANA Notes* (December 2007). This issue of *Notes* is available for viewing or download at www.ANAUSA.org.

⁷ “Role of the Neurofibromatosis Type 2 Gene in the Development of Tumors of the Nervous System,” *Neurosurg. Focus*, 19 (2005).

“The Language of Life”

Anyone interested in investigating and thinking about genetic, environmental and lifestyle risk factors for human diseases would do well to begin by reading Dr. Francis S. Collins’ *The Language of Life: DNA and the Revolution in Personalized Medicine* (2010). This is an important book by a leading figure in the field of molecular genetic research. It’s easy reading with fascinating personal and patient stories and a practical Appendix for definitions of terms and a helpful “Genetics 101.” Dr. Collins established his reputation as a dedicated ‘gene hunter’ beginning in the 1980s. He participated importantly in the discovery of the gene for cystic fibrosis (1989) and his own scientific laboratory later



identified the NF1 gene and protein product *neurofibromin* for Neurofibromatosis Type 1 (1990), a condition that usually causes benign tumors (neurofibromas) on nerves under the skin. Dr. Collins spent fifteen years (1993-2008) as Director of the National Human Genome Research Institute (NIH) and in 2008 he was awarded the National Medal of Science. Since 2009 he has been Director of the National Institutes of Health (NIH). His impressive credentials will encourage readers to pay careful attention to the ‘heads-up’ he presents about major advances in medicine due to the unlocking of the secrets of DNA. He writes (in Chapter 3, “Is It Time to Learn Your Own Secrets?”): “Recent discoveries place us in a position to make several strong statements: (1) for each disease, specific genetic and environmental risk factors exist, and are rapidly being identified; (2) these discoveries are providing powerful new insights into both treatment and prevention; (3) the more you know about all this, the more you can adjust your own lifestyle and medical surveillance to prevent illnesses or catch them in early and treatable stages.”

(To be continued, next issue)

ANA Patient Survey, 2012

The September 2013 issue of *ANA Notes* reports briefly on the results of ANA’s 2012 online survey of acoustic neuroma patients. The full “2012 Survey Results” can be viewed or downloaded at www.ANAUSA.org.

The survey was responded to by 1,338 patients, compared to 2,004 for the earlier 2007-08 survey. The primary symptoms reported in 2012 remained similar, with hearing loss (88%), tinnitus (74%) and balance disturbances (63%) still leading the list. The 2012 percentages were lower for fatigue (25%), depression (14%) and memory difficulties (20%). For Quality of Life following diagnosis, the 2012 report states: “Almost all the respondents (88%) indicated they were able to continue regular employment and/or activities after their diagnosis and 72% indicated they were still employed in the same capacity or perform the same activities today.”

The following tables are excerpted from the 2012 report:

Tumor Size at Diagnosis (% of respondents)			Type of Treatment (% of respondents)		
Size	2012	2007-08	Treatment	2012	2007-08
1.5 cm or less	43	38	Microsurgery	50	61
1.6-2.5 cm	25	27	Wait-and-Watch	26	20
Larger than 2.5	20	27	Radiation	24	20

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The Executive Board of ANA/NJ gratefully acknowledges the following who have contributed to ANA/NJ in support of its mission to provide information, encouragement and support to acoustic neuroma patients and their families.

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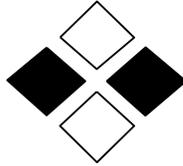
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Spring 2014 Chapter Meeting

*“Caring and Sharing”
An Open Meeting for Patients, Family & Friends*

Sunday, April 6, 2014
1-3:30 pm

Mercer County Library System
Lawrenceville Branch
2751 Brunswick Pike (Route 1 South)
Lawrenceville, NJ 08648
609-882-9246

Refreshments Social Time

Directions to the Library

From North Jersey: Take Route 1 South. After the I-295 overpass there will be a traffic light at Franklin Corner Rd. Stay to the right onto Business Route 1 and make a quick right at the traffic light onto Darrah Lane. The Library is on the right.

From Trenton: Take Route 1 North to the Whitehead Rd Exit. Make a left onto Whitehead Rd and follow until the traffic light. Make a right onto Business Route 1 and continue North about one mile. Immediately after the third traffic light, move into the jug-handle to cross Route 1 onto Darrah Lane. The Library is on the right.

From Eastern NJ: Take I-195 West to I-295 North. Exit at Route 1 South. Follow the “From North Jersey” directions above.

From South Jersey: Follow I-295 North. Exit at Route 1 South. Follow the “From North Jersey” directions above.

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