Towards Better Treatment of Vestibular Schwannomas

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Vestibular schwannomas (VS) are tumors of the vestibular nerve sheath that cause tinnitus, progressive sensorineural hearing loss, disequilibrium, hypesthesia, facial paralysis and, rarely, brainstem compression and death. Quality of life if compromised. The gene responsible for producing Merlin, also known as neurofibromatosis type 2 (NF2), was identified in 1993 and its mechanisms of activity studied vigorously to determine the potential treatment pathways to correct for loss of this tumor suppressor gene. Unilateral VS develop when a somatic mutation occurs, however, if a mutation occurs in the NF2 gene in the germline, either from a de novo pathologic variant, or inherited from a parent, neurofibromatosis type 2 occurs which is highly penetrant.

NF2 is characterized by bilateral vestibular schwannomas, with 70% of patients also developing spinal cord tumors (schwannomas, meningiomas or ependymomas) and 50% of patients developing meningiomas.

Treatment options for sporadic unilateral vestibular schwannomas include observation, stereotactic radiation and microsurgery. No approved drugs are available. A trend toward observation for growth patterns has emerged over the past decade prior to active treatment when the tumors pose no threat the brainstem compression. With microsurgery and radiotherapy, facial nerve preservation is probable, but hearing preservation continues to be a challenge with any treatment option. Patients with NF2 are particularly affected. Our experience with cochlear implants and auditory brainstem implants will be reviewed.

Mechanisms of hearing loss have traditionally been thought to be related to cochlear nerve compression or vascular compromise, but more recent data shows excretion of exosomes from tumors which may affect the hearing. Additional information regarding cochlear synaptopathy in NF2 patients may account for some degree of hearing loss in addition to tumor invasion into the cochlea and cochlear nerve.

Drug trials undertaken for the treatment of NF2–associated tumors to date are numerous. Bevacizumab has been the most widely used off-label with demonstrated decreased tumor volumes and hearing improvement in 30–50% of patients. Current clinical trials include brigatinib, AR-42 and aspirin in which we participate.

We are encouraged by the increasing number of successful gene therapy trials for a number of human conditions and believe that NF2 as a single gene disease may be a good candidate and we are working toward the goal of improved treatment of NF2, and potentially for sporadic VS and meningiomas as well.

A review of progress toward better treatment of VS over the past 30 years with emphasis on recent advances will be presented.