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Audiologic and radiographic response of NF2-related vestibular schwannoma to erlotinib therapy

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SUMMARY

Background A 48-year-old man presented to a neurologist with complaints of bilateral hearing loss and tinnitus. The patient was a member of a large family affected by neurofibromatosis type 2 and first noted hearing loss 10 years before presentation.

Investigations Medical and neurological examination, MRI scan of the brain and spinal cord, pure-tone audiometry, NU–6 monosyllabic word test with phoneme scoring, City University of New York topic-related sentences test, noise/voice test of minimal auditory capability battery.

Diagnosis Progressive neurofibromatosis-type-2-related vestibular schwannomas.

Management Annual cranial MRI and audiology, surgical resection of right vestibular schwannoma, high-power behind-the-ear hearing aid, erlotinib therapy for progressive left vestibular schwannoma.

KEYWORDS erlotinib, neurofibromatosis, schwannoma, vestibular

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Learning objectives

Upon completion of this activity, participants should be able to:

1 List the types of tumors associated with neurofibromatosis type 2 (NF2).
2 Describe the birth incidence of NF2.
3 List the 191 National Institutes of Health (NIH) criteria for the diagnosis of NF2.
4 Describe the treatment indications and options for NF2.
5 Identify the potential use of erlotinib in patients with NF2.

Competing interests

The authors, the Journal Editor L Hutchinson and the CME questions author D Lie declared no competing interests.

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THE CASE

A 48-year-old man presented to a neurologist for comprehensive evaluation. The patient complained of bilateral hearing loss and tinnitus, which he had first noted 6 months before presentation. He initially experienced hearing problems 10 years earlier, and 8 years before presentation he visited his primary care physician for hearing evaluation. Auditory testing at that time demonstrated bilateral sensorineural hearing loss that was attributed to occupational noise exposure. Over the following 8 years, the patient experienced progressive decline in hearing and developed persistent imbalance.

At the time of presentation, the patient had a medical history of pancreatitis, renal calculi, and anxiety. He smoked approximately one-and-a-half packs of cigarettes per day and denied

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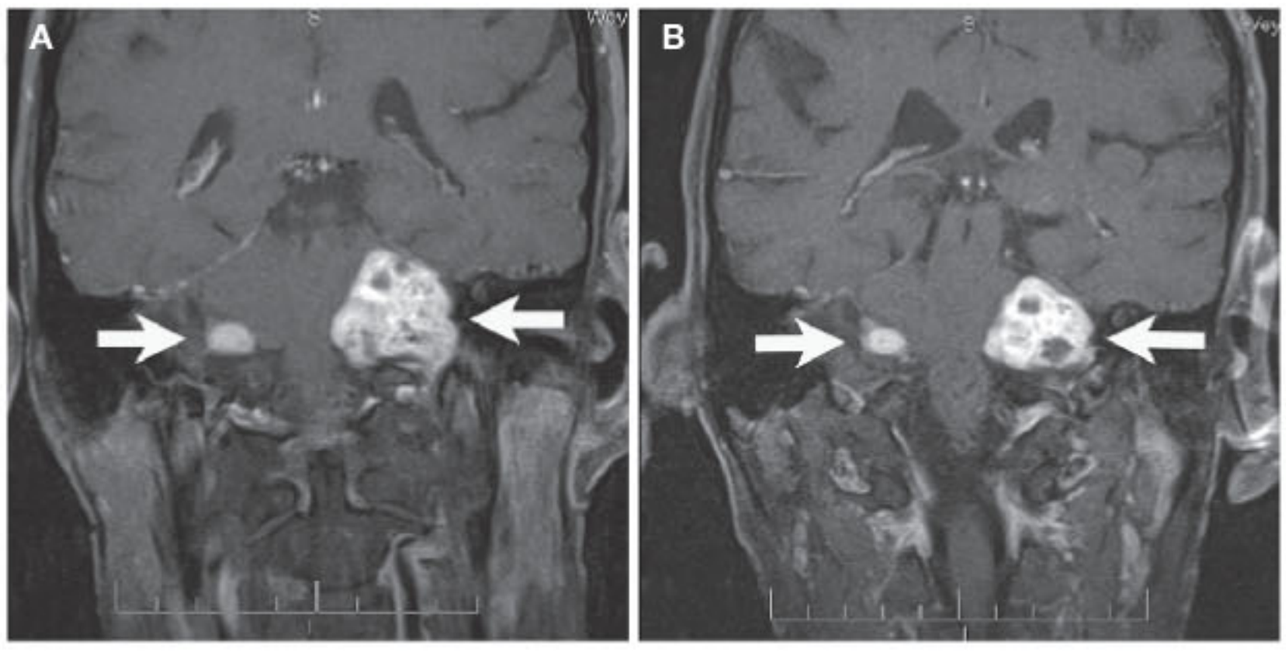

Figure 1 Cranial MRI scans of the patient before and after treatment with erlotinib. (**A**) A post-contrast T1-weighted coronal MRI scan of the patient before erlotinib therapy. The arrows indicate bilateral vestibular schwannomas characteristic of neurofibromatosis type 2. (**B**) A repeat MRI scan after 11 months of erlotinib therapy showing the decreased size of the left vestibular schwannoma.

alcohol use. The patient was a member of a large family with a history of neurofibromatosis type 2 (NF2): his father and two siblings had been diagnosed with NF2. Elemental neurological examinations, including testing of cranial nerves, power, sensation, coordination, reflexes, and gait, were normal. Audiologic evaluation revealed symmetric hearing loss with pure-tone thresholds of 45 decibels hearing level (dBHL) at 250 Hz, 65 dBHL at 500 Hz, 70 dBHL at 1,000 Hz and 75 dBHL at 2,000 Hz (normal range 0–20 dBHL). The patient's word recognition was 48% in the right ear and 72% in the left ear. Brain MRI revealed bilateral vestibular schwannomas, each measuring 2.1 cm along the long axis, and the patient was diagnosed with NF2. No other enhancing lesions were identified. MRI of the cervical spine revealed a 5 mm focus of T2 hyperintense signal at C5–6, which enhanced after the administration of gadolinium contrast.

The patient was followed annually with cranial MRI and audiology. During the 7 years following presentation, he experienced gradual bilateral hearing loss due to progressive tumor growth. An MRI scan 7 years after diagnosis demonstrated severe brainstem compression and he underwent resection of the right vestibular schwannoma with post-operative anacusis in the affected ear. Over the next 7 years he lost hearing in the contralateral ear, and his MRI revealed significant brainstem compression related to growth of his left vestibular schwannoma. Audiometric testing up to 125 dBHL elicited no responses at any frequency. The patient, hoping to avoid further surgery, sought opinions regarding treatment options. Radiation therapy was not recommended because of the risk of brainstem herniation during treatment. After lengthy discussions, the patient opted for treatment with erlotinib on the basis of preclinical evidence suggesting an anti-proliferative effect in *Nf2*-deficient cells.[1] He started receiving 150 mg erlotinib daily for progressive vestibular schwannoma. The patient was seen monthly by his oncologist for the first 3 months, and then quarterly, with monthly visits to his internist for medical examination, and complete blood counts and chemistry panels. Cranial MRI and audiology were performed every 3 months to monitor response to treatment. Volumetric MRI analysis was performed on all available MRI scans taken during the past 7 years to determine tumor size before and after treatment with erlotinib.[2]

Within 3 months of starting erlotinib therapy tumor volume in the left vestibular schwannoma stabilized (Figure 1) and the patient reported perception of loud noises. By 6 months, his left vestibular schwannoma decreased in volume and audiological examinations documented perception of pure-tone thresholds at low frequencies. At month 10, he began to use his hearing aid and reported hearing voices. After 11 months of erlotinib therapy, the tumor had reduced in volume by 12% (Figure 2) and the patient reported speechreading ability in face-to-face settings when using his hearing aid.

During the 11 months of therapy, the patient tolerated erlotinib well with only occasional episodes of grade 1 diarrhea, as rated by the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE 3.0). He denied rash or nausea. The patient experienced recurrent arterial thrombi in the femoral arteries related to his pre-existing vascular disease. Laboratory examinations identified a subtherapeutic international normalized ratio <2.0 on routine coagulation studies at the time of thrombosis. At no point did the results of safety tests exceed institutional limits.

After 11 months of therapy, the patient underwent detailed pure-tone audiometry[3] and was tested for word recognition, speechreading ability, and noise/voice discrimination in order to confirm the re-emergence of useful hearing ability. Pure-tone audiometry demonstrated tone percepts for frequencies from 250 Hz (80 dBHL) to 1,000 Hz (100 dBHL) in the left ear. These percepts were verified as tonal as

opposed to vibrotactile responses.[4] His ability to recognize words was tested using the NU–6 monosyllabic word test with phoneme scoring list 2B (110 dBHL). He correctly identified 15 phonemes (10%), which exceeded the *a priori* probability of identifying 6 phonemes (4%) by chance.[5] In addition, he identified 1 word (2%) correctly, which would not be expected to occur by chance.

The patient was then tested with his hearing aid in place (approximately 127 decibel sound pressure level in the ear). He was first tested with the minimal auditory capability battery noise/voice test using a calibrated speaker at the distance of 1 m.[6] This test requires that a patient distinguish between a spoken sentence and a sentence-like series of noises, and is the least demanding test of auditory information. The patient correctly identified the noise versus voice for 56% of items, which exceeds the *a priori* probability of correctly distinguishing 50%.[6] The patient's ability to speechread face-to-face using his hearing aid was verified using the City University of New York topic-related sentences test.[7] He accurately recognized 60% of words from sentence block 7 when this text was read by his wife but, as expected, could only recognize 10% of words when the text was read by an unfamiliar speaker on the standard-test videodisk. The patient could not perform the task without his hearing aid. Together, these audiometric results document modest levels of usable hearing in the left ear. The patient continues to receive erlotinib 19 months after the initiation of treatment and has maintained his current level of hearing function without evidence of tumor growth. His current health status is unchanged and he will remain on erlotinib for as long as he maintains a clinical response without significant toxicity.

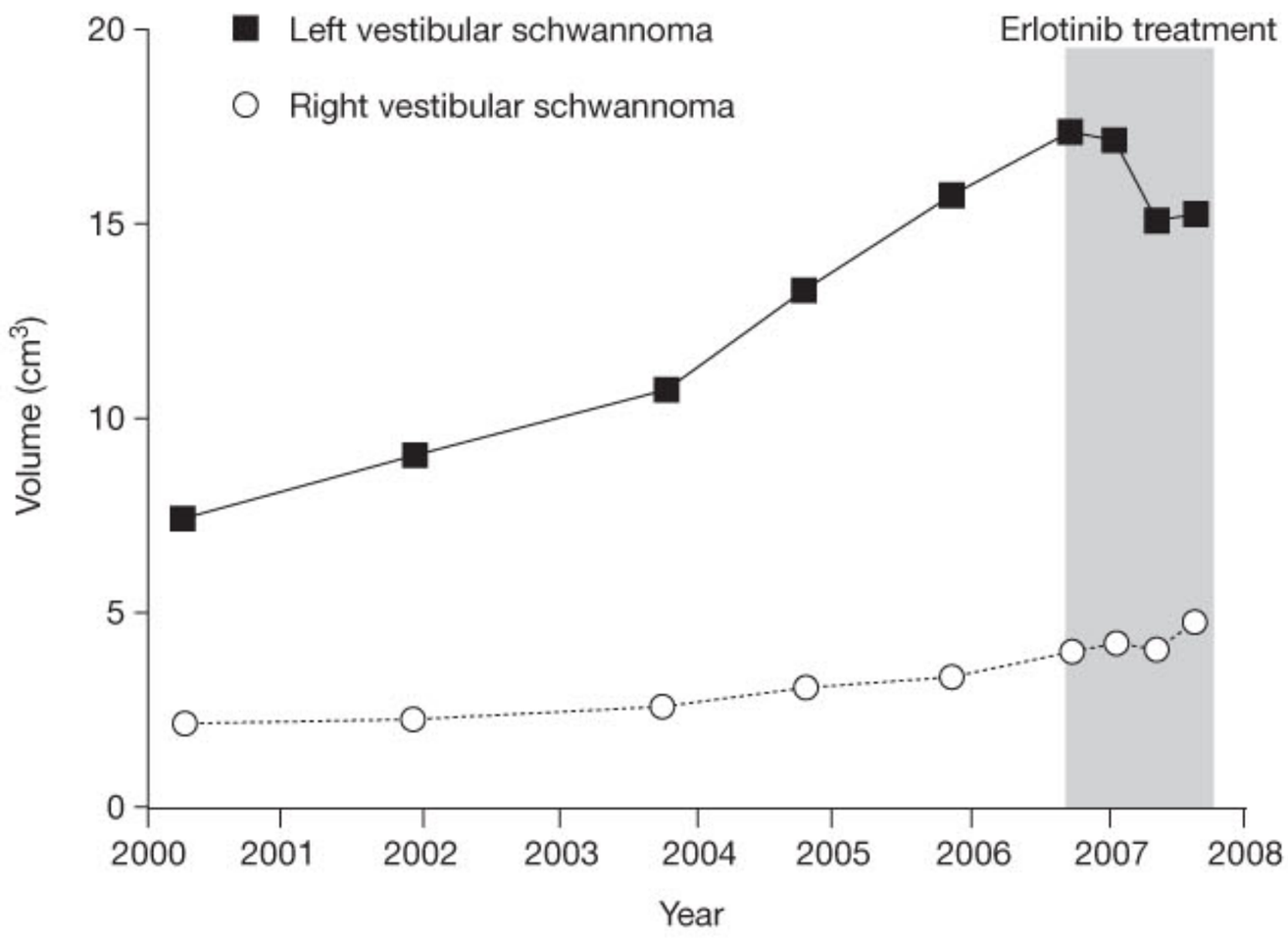

Figure 2 Volumetric analysis of bilateral vestibular schwannomas. A graph of the tumor volume (cm^3) as determined by longitudinal MRI. The shaded area indicates the period in which the patient was receiving erlotinib.

DISCUSSION OF DIAGNOSIS

NF2, previously called central neurofibromatosis, is a tumor-suppressor syndrome characterized by the presence of schwannomas, meningiomas, and spinal cord gliomas.[8] NF2 is transmitted in an autosomal dominant fashion, with a birth incidence of 1 in 25,000.[9] Symptoms of eighth cranial nerve dysfunction, including deafness, tinnitus, or imbalance, typically appear at 17–21 years of age.[8] In children, symptoms can include non-vestibular cranial nerve dysfunction, myelopathy, seizures, skin tumors, and juvenile cataracts.[8] The NIH consensus criteria for diagnosis of NF2, established in 1987 and revised in 1991, require either the presence of bilateral vestibular schwannomas or a family history with unilateral vestibular schwannoma and any one of the following: meningioma; glioma; neurofibroma; schwannoma; or posterior subcapsular opacities.[10,11] Alternative diagnostic criteria, such as the Manchester criteria or the National Neurofibromatosis Foundation criteria, have been proposed.[12] Initial evaluation of individuals with NF2 should include a complete family and medical history; neurologic, audiologic, ophthalmologic and skin examinations; and MRI scans of the brain and spinal cord.[13] Asymptomatic patients with NF2 but without tumors should have MRI screening of brain and spinal cord every 2 years between the ages of 12 years and 20 years and every 3 years thereafter.

TREATMENT AND MANAGEMENT

The standard treatment options for bilateral vestibular schwannomas include surveillance, surgical resection, and radiation therapy. Patients under surveillance are generally followed annually with MRI scans and audiological examinations.[13] Hearing aids prolong the period of useful hearing but deafness is the rule for patients who do not undergo hearing-sparing surgery; however, watchful waiting might result in longer periods of useful hearing for many patients with

larger tumors because attempts to debulk these schwannomas can produce deafness.

The surgical management of bilateral vestibular schwannomas is the treatment approach that has been studied more thoroughly than others. The goal of surgery is to either preserve hearing (for small tumors) or to treat brainstem compression and/or hydrocephalus (for large tumors).[8] In addition, surgery opens the possibility of placement of an auditory brainstem implant in selected patients. The auditory brainstem implant is a prosthetic device that bypasses the cochlea and the auditory nerve to transmit auditory information directly to the brainstem.

Hearing preservation is a reasonable goal for lesions less than 1.5 cm in size that are not multilobulated. Hearing preservation rates following tumor resection via a middle cranial fossa approach are about 70% at specialized centers.[14] Unfortunately, most tumors do not meet these criteria at presentation, and surgery for hearing preservation is not possible. Thus, it is highly desirable to identify affected individuals early in life so that hearing-sparing surgery can be offered.

For tumors greater than 1.5 cm or those that are multilobulated, the ability to preserve hearing after resection is low. In general, tumor resection in a hearing ear should be deferred until the development of neurologic symptoms, increased intracranial pressure, or impending hydrocephalus. Tumor resection in a nonhearing ear should be performed as clinically indicated, with a focus on preserving other cranial nerve function.[8]

Radiation therapy for vestibular schwannomas has become more popular in recent years. Stereotactic radiosurgery in NF2 is associated with actuarial local control rates of 85% at 5 years and 81% at 10 years.[15] The measurable hearing preservation rate is about 40% with a 20% risk of deafness in patients with serviceable hearing before treatment.[16] Other potential complications of stereotactic radiosurgery include facial weakness, trigeminal neuropathy, and vestibular dysfunction.[15] In addition, there is emerging evidence that patients with tumor-suppressor syndromes who receive therapeutic radiation are at increased risk for developing a secondary malignancy years after treatment.[17] Although this association is more robust for NF1 than for NF2, patients should be cautioned about potential adverse effects before they receive radiation therapy.

For many years there has been intense interest in developing chemotherapy for patients with NF2. Recently, Curto and colleagues have shown that loss of *Nf2* in primary cells leads to failure of contact-dependent inhibition of proliferation.[1] By use of a combination of laboratory techniques, the group showed that, under normal conditions, the NF2 protein Merlin associates with EGFR (also known as ErbB1) via the scaffold protein NHERF1 and prevents signaling from the activated EGFR. In the absence of functional Merlin, EGFR signaling cannot be down-regulated and *Nf2*-deficient cells proliferate despite the presence of cell-to-cell contact. Treatment with EGFR inhibitors, such as erlotinib or gefitinib, prevents the over-proliferation of these cells.[1]

This case report represents the first successful laboratory-to-clinic translation of research on NF2. This patient was offered treatment with erlotinib because this drug has been well studied in clinical oncology and is approved by FDA for treatment of non-small-cell lung cancer.[18] Serious complications are rare and in patients who respond to treatment, long-term therapy with this agent is well tolerated—the discontinuation rate because of the development of adverse effects is approximately 5%.[18] Importantly, the drug is orally administered. The patient's audiologic and radiographic response to treatment was clinically significant, with a decrease in tumor volume and the re-establishment of useful hearing. These findings justify a prospective clinical trial of erlotinib for NF2-related vestibular schwannomas. Such a trial should include standardized assessments of tumor volume and hearing, which would allow confirmation of the clinical benefit of erlotinib treatment before this agent enters widespread use in the community.

CONCLUSIONS

This is the first case report demonstrating therapeutic activity of erlotinib for progressive vestibular schwannoma in NF2. These data suggest that targeted therapies might be effective for NF2-related tumors and that hearing loss related to progressive vestibular schwannomas might be reversible in selected circumstances. Prospective clinical trials are warranted to determine the optimum dose and duration of erlotinib treatment for progressive vestibular schwannomas in NF2 and to study the efficacy of this agent in other NF2-related tumors.

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Competing interests

The authors declared no competing interests.