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Response of recurrent anaplastic ependymoma to a combination of tamoxifen and isotretinoin

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Standard treatment for brain ependymomas includes surgery followed by focal radiotherapy when resection is incomplete. The role of chemotherapy for recurrent unresectable anaplastic ependymomas previously treated with radiotherapy is unsettled.1 We report an adult patient with a recurrent and multifocal anaplastic brain ependymoma who responded to the association of tamoxifen and isotretinoin.

**Patient.** A 39-year-old man developed severe headaches in June 1997. A brain CT and MRI disclosed the presence of mild hydrocephaly and a right bulbopterygoidal heterogeneous tumor which enhanced after contrast infusion. A ventriculoperitoneal derivation was performed followed by an incomplete resection of the tumor. Histologic analysis revealed an anaplastic ependymoma. Focal radiotherapy (60 Gy) using conventional 2-Gy fractions was delivered between August 12, 1997, and September 23, 1997. In June 1998, the patient had recurrent headache and altered equilibrium and an MRI showed a heterogeneous enhancing lesion at the lateral edge of the pons invading the fourth ventricle and right cerebellum. Treatment with temozolomide (200 mg/m²/day 5 days every month) was initiated in August 1999. Clinical and radiologic stabilization was achieved, lasting until January 2000, after 17 courses of temozolomide, when clinical deterioration occurred with exacerbation of gait ataxia. A new MRI showed the protuberant lesion unchanged but two new enhancing lesions measuring less than 1 centimeter in the right temporal lobe. A second-line chemotherapy was initiated with carboplatin (350 mg/m²/month) leading to a 4-month stabilization. In July 2000, a progression of the temporal lesion was found on MRI. A single course of BCNU (150 mg/m²) was delivered in October 2000 with grade III hematologic toxicity in the setting of continuous clinical and radiologic deterioration. In February 2001 (figure, A), a daily treatment with tamoxifen (200 mg/day) was started, combined 2 months later with isotretinoin (80 mg/m²/day for 3 weeks, followed by 1 week of rest). MRI started to show clear signs of improvement in September 2001 and a complete regression of the temporal lesion was observed in November 2001, while corticosteroids were tapered from 48 mg/day of methylprednisolone in April 2001 to 8 mg/day in September 2001. In March 2002, a complete response persisted on MRI (figure, B) with no clinical counterpart while the patient was off corticosteroids. In July 2002, in the setting of radiologic and clinical stability, the treatment with tamoxifen and isotretinoin was discontinued, but 2 months later a new MRI scan revealed the recurrence of the enhancing lesion in the right temporal lobe.

**Discussion.** In patients with unresectable recurrent anaplastic ependymomas previously treated with radiotherapy, chemotherapy represents the only option. Only a few cases of complete responses have been reported with various agents, particularly platinum-based regimen and a combination of vincristine and cyclophosphamide.2,3

Although our patient did not respond to carboplatin and BCNU, he experienced long-lasting stabilization with temozolomide and a striking response to the combination of tamoxifen and isotretinoin. Five patients with ependymomas treated with temozolomide have been reported; three presented a partial response, one a minor response, and one stabilization.4 Tamoxifen, a protein-kinase C inhibitor, has showed some effect in some patients with gliomas.5 In ependymomas, a 24-month stabilization was reported in a 5-year-old boy with anaplastic ependymoma following high-dose oral tamoxifen alone.6 Although retinoids have shown growth inhibitory and differentiating effects on glioma cell lines, clinical trials as a single agent have been disappointing.7

In the absence of histologic diagnosis of the recurrent tumor, a radionecrosis cannot be ruled out in this patient. However, this seems unlikely because he received conventional irradiation and fractions (50 Gy in average over the temporal regions where the lesions appeared as compared to 60 Gy over the brainstem where no lesions occurred) and had no predisposing factor for radiation damage (he was young and did not receive concomitant chemotherapy). In addition, the lesion disappeared in the setting of a relatively rapid tapering of corticosteroids, a very unusual feature for unresected radionecrosis, and did not recur during 6 months in the absence of steroids. Finally, the tumoral nature of the lesion is supported by its recurrence 2 months after discontinuation of the treatment with tamoxifen and isotretinoin.

This observation raises the question of a possible benefit of the combination of tamoxifen and isotretinoin in unresectable malignant ependymoma recurring after radiotherapy and standard chemotherapy.

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References
3. Duffner PK, Krischer JP, Sanford RA. Prognostic factors in infants and

Sensorineural hearing loss: A reversible effect of vigabatrin

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Vigabatrin, a GABAergic antiepileptic drug, has been used successfully for the treatment of patients with partial epilepsy. Vigabatrin irreversibly inhibits γ-aminobutyric acid (GABA) transaminase with resultant increased concentrations of GABA in the brain and retina.† Visual field concentric constriction secondary to vigabatrin is a frequent side effect and in most cases is irreversible‡. It has been speculated that the underlying mechanism is either a direct effect of vigabatrin on the ganglion cells of the retina or a cytotoxic effect of a possible increased GABA concentration on retina cells.† There have been no reports of an association between the use of vigabatrin and sensorineural hearing loss. We report a patient who developed progressive hearing loss and visual field constriction after 4 years of therapy with vigabatrin for partial epilepsy.

Case report. A 14-year-old boy with a 9-year history of partial epilepsy presented to the University Neurology outpatient clinic at the end of July 2002 with a moderate (50 to 55 dB HL) bilateral sensorineural hearing loss and bilateral visual field constriction. The rest of the neurologic examination as well as the general physical examination were unremarkable. Pregnancy, delivery, and physical and mental development were normal. There was no history of head injury or neurotoxic drug use other than the antiepileptics. He had a 15-year-old sister with a long-standing history of partial epilepsy well controlled with vigabatrin and sodium valproate. At age 9, she had been diagnosed with neurofibromatosis. Her clinical examination revealed cutaneous café au lait spots, subcutaneous neurofibromas, and a Lisch nodule in the left iris, compatible on clinical grounds with the diagnosis of neurofibromatosis type 1.

In August 1994, after a generalized tonic-clonic seizure, the patient was admitted to the University Department of Pediatrics. On admission, the general physical examination including otorhinolaryngologic and ophthalmologic examination had normal results. Full routine blood tests and EEG had normal results, as did brain CT scan. The EEG confirmed the diagnosis of partial epilepsy and he was discharged home on carbamazepine therapy. For the next 3 years, the epileptic seizures were unsatisfactory controlled with a combination of carbamazepine and sodium valproate; in 1999, carbamazepine was discontinued and vigabatrin was added to sodium valproate. Gradual increase of vigabatrin up to 3000 mg/day proved to be successful treatment and over the last 3 years the patient remained free of seizures.

In February 2002, his mother noticed that he had developed some degree of bilateral hearing loss, which on March 12, 2002, was confirmed by an audiogram (figure, A). Otoscopy and a tympanogram had normal results. On April 12, 2002, repeat audiogram showed deterioration of hearing loss (figure, B) and the patient began using hearing aids in both ears. On June 26, 2002, a visual field examination, suggested by his pediatrician, showed bilateral concentric constriction. Visual acuity, funduscopy, and visual evoked potentials were normal. The next day, vigabatrin was discontinued and he remained on sodium valproate monotherapy. Repeated audiograms on June 6, 2002; July 22, 2002 (not shown); and July 25, 2002 (figure, C) showed no change in hearing loss. Weber test, Rinne test, and tympanogram results were normal. The auditory reflexes were present at 100 dB HL as was expected by the degree of hearing loss and the brainstem auditory evoked potentials in 90 dB HL were normal.

Owing to his sister’s neurofibromatosis, skin examination with Wood lamp was performed, without abnormal findings. A high-resolution brain MRI (gadolinium enhanced) on July 3, 2002, focusing on the brainstem, was normal, ruling out eighth nerve tumors. Ten weeks after the discontinuation of vigabatrin, the patient remained free of seizures; his visual field defects persisted, but the hearing loss had almost completely recovered and hearing aids were no longer required (figure, D).

Discussion. In the current case, the mode of onset of hearing loss, the equal impairment of all frequencies, shown by the audiograms (figure), and the remaining neuro-otologic investigations suggest moderate panocholear damage. The recovery of the hearing loss within 2 months of vigabatrin discontinuation suggests that it was probably caused by vigabatrin. This might be explained by a cytotoxic effect of vigabatrin on the cochlear inner and outer hair cells although a potentiation by the concurrent GABAergic valproate administration cannot be excluded. It could be speculated that the underlying mechanism for the hearing loss in this case is increased GABA or its metabolite glutamate concentrations in the cochlear inner and outer hair cells. In vitro and in vivo animal studies have shown that GABA is an important inhibitory neurotransmitter for the function of the cochlear inner and outer hair cells.© This report shows that a reversible panocholear sensorineural hearing loss in association with vigabatrin therapy may be a rare side effect.

† Died May 10, 2003.
‡ Died November 1, 2002.

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References

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