

Article ▶ Esotropia Induced by a Chemotherapeutic Agent in a Patient with a Brain Tumor

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ABSTRACT

Patients who present with a sudden onset esotropia require a complete eye examination with dilation and cycloplegia to differentiate an accommodative from a non-accommodative cause. Non-comitancy, motility dysfunctions, and optic nerve anomalies must be ruled out. Cases of non-accommodative esotropia are often idiopathic but may be associated with neurologic problems.

This paper will present a case report of a 6-year-old male who presented with a sudden onset esotropia. He had a prior history of surgical resection of an ependymoma and was currently under treatment with a chemotherapeutic agent. Treatment options for the esotropia are presented.

Keywords: brain tumor, ependymoma, esotropia, etoposide, pediatric

Introduction

Most patients with esotropia are diagnosed before the age of 5.¹ Non-accommodative esotropia is characterized by a moderate to large angle of deviation at distance and near without signs of extraocular muscle paresis.¹ Cases of non-accommodative esotropia can develop acutely and may be associated with seizures, fevers, and brain tumors.^{2,3}

Ependymomas are brain tumors of neuroectodermal origin that arise from ependymal cells of the ventricles and the central canal of the spinal cord.⁴ They are the third most common type of brain tumor in children, comprising approximately 5-12% of pediatric brain tumors.^{4,7} In children, the mean age at diagnosis is 4-6 years.⁶⁻⁸ Some studies have found no gender predilection, while others have found a slight male predominance.⁶⁻⁸ The annual incidence of ependymomas is 2/1,000,000.⁷ In the United States, approximately 200 cases are diagnosed annually.⁹ In children, approximately 90% of tumors are intracranial, while in adolescents and adults, 75% arise in the spinal canal.⁸

Patients may initially present with headache, nystagmus, nausea, vomiting, ataxia, lethargy, papilledema, or cranial nerve palsies. Infants may present with a bulging fontanelle or enlarging head circumference.^{7,8,10,11}

The following report describes a patient with a history of a previously treated ependymoma who presented with an acute onset esotropia that was believed to be secondary to a chemotherapeutic agent.

Case Report

A 6-year-old white male was referred by his primary care doctor for an evaluation of strabismus. Mom reported that 5 months prior, the patient began complaining of blurry vision and began closing his right eye when viewing an object. At the same time, his right eye started turning in. The eye turn was variable and more pronounced when the patient was tired. The parents did not notice any abnormal head turns or tilts.

The patient's past medical history was significant for a posterior fossa ependymoma, grade 2 on initial diagnosis, diagnosed 5 years prior (age 1). He underwent a surgical resection of the tumor in the month of diagnosis and received radiation therapy. Two years later (age 3), the tumor recurred, and the patient underwent a repeat surgery and a second course of radiation at another institution. Two years later (age 5), the tumor was thought to be recurring, and a third operation was undertaken; however, pathology was consistent with radiation necrosis, and there was no evidence of an active tumor. Five months prior to the eye exam, the patient was started on chemotherapy, specifically etoposide 50mg.

The patient was initially examined by a pediatric ophthalmologist. At the time of the initial eye exam, an MRI of the brain, performed the same day, showed a stable mass in the "left pontomedullary region measuring 2.6 x 2.5 x 2.5 cm with moderate enlargement of the lateral and third ventricles." (Images from the MRIs were not available for review at the time this paper was being prepared.)

The patient's current medications included celecoxib (Celebrex®, Pfizer Inc., Mission, KS) 50 mg bid, etoposide 50 mg daily, lansoprazole (Prevacid®, Takeda Pharmaceuticals, Deerfield, IL) 15 mg daily, and dexamethasone 0.5 mg bid.

Eye examination revealed 20/25 acuity in each eye. A comitant esotropia of 50 prism diopters was noted at distance and near. The patient did not appreciate the stereo fly. A fast upbeat vertical nystagmus was present in upgaze. There were no motility restrictions. Pupils were equal, round, and reactive without evidence of a relative afferent pupillary defect. Visual fields were full to a peripheral target in each eye. A dilated exam revealed a healthy optic nerve without edema and healthy retinae without radiation retinopathy. Cycloplegic refraction revealed +0.25 sphere in each eye. The ophthalmologist felt that this case was non-surgical and referred the patient to optometry for therapy.

Follow Up

The patient returned for a one month follow up with the optometrist. The medical history was unchanged. Additional questioning revealed that the eye turn was most noticeable 7 days after the patient started his 21-day course of etoposide, improving, but not fully resolving, when he was not taking the medication. His mother reported that she suspected that the patient had problems reading books at near because of changes to his working distance.

At this follow up examination, visual acuity was 20/20 (6/6) OD, 20/20 (6/6) OS. Cover test found an intermittent, comitant, right esotropia at distance and near. The maximum deviation was 40 prism diopters at distance and 50 prism diopters at near. At times the patient was orthophoric. There was no change in the magnitude of the deviation with +3.00 lenses OU. No "A" or "V" pattern was present. Retinoscopy revealed +0.25 each eye, and dynamic retinoscopy, over +0.25 OU, revealed +1.00 in each eye.

In-office therapy was not an option because the patient resided 4 hours traveling distance from the clinic, and there were no vision therapy providers located near where the patient resided. Due to the lag of accommodation and larger magnitude of the esotropia at near, the patient was prescribed +1.00 for near tasks. He was also told to patch the left eye 2 hours per day and was given activities to improve abduction of the right eye. He was told to follow up in 2 months.

Follow Up 2 Months Later

At the follow up visit, his mother reported that she felt that the eye turn was less noticeable than at the prior exam. He was doing well with patching and was using the glasses for prolonged near work. The patient was no longer complaining of blurry vision at near.

The patient's medical history was significant for a change in the steroid to hydrocortisone 25 mg daily. Visual acuity was unchanged. Cover test revealed an intermittent right esotropia of 25 prism diopters at distance, 30 prism diopters at near. Again, the patient was occasionally orthophoric. Worth 4 Dot showed OD suppression at distance and near.

Binasal occluders were added to the patient's lenses as a new therapeutic treatment. The patient was asked to use the glasses with the binasals for 2 hours per day while performing tasks requiring eye-hand coordination such as drawing, ball tossing, popping bubbles, playing with Legos,[®] etc. The patient was also asked to continue patching the left eye 1-2 hours per day but was not to use the binasals when patching. He was asked to follow up in 4 months.

Follow up 4 Months Later

Again, at this visit, his mother reported that the patient was doing well. The medical history was significant for a change in the steroid back to dexamethasone due to side effects from hydrocortisone. An MRI was done 1 month prior to the exam and showed no change in the tumor size from the prior

imaging. The patient was using the glasses for near work and was working on eye-hand tasks while wearing binasals. He was doing well with the patching 1-2 hours per day.

Visual acuity and alignment were unchanged from the prior exam. With 15 prism diopters of Fresnel prism base out right eye, the esotropia was reduced to 8 prism diopters at distance and near. In an attempt to help with binocularity, the patient was told to discontinue the binasal occluders and was given Fresnel prisms to wear while doing binocular tasks. He was told follow up in 4 months. His mother offered to video or photograph the patient's eyes during the course of his etoposide treatment so that the change in the magnitude of the alignment could be observed.

Approximately 6 months after the last visit, the patient experienced a recurrence of the tumor and subsequent surgery in an attempt to excise it. Approximately four months after the surgery, an MRI revealed that the tumor had metastasized to the brain and spinal column. The patient was placed in hospice care and passed away a few weeks later.

Discussion

Treatment:

The treatment of ependymomas is "one of the most controversial in pediatric oncology" and can include any combination of surgery, radiotherapy, and chemotherapy.^{4,5} Currently, the standard treatment is surgery with post-operative radiotherapy or chemotherapy, depending on age.

The goal of surgery is gross total resection, which is achieved in 40-60% of patients.^{4,7} Gross total resection is confirmed by Magnetic Resonance Imaging (MRI) results and surgical report.⁷ The extent of tumor removal is considered by many to be the most important predictor of prognosis. In spite of imaging from MRIs, microscopic areas of remaining tissue may not always be detected. Recent advances in surgery, including ultrasound guided neurosurgery, may improve surgical success rates.⁴ Side effects of surgery include cerebellar mutism, cranial nerve defects, and vision impairment.⁷

Chemotherapy is frequently used in children less than 3 years of age due to concerns about the possible side effects of radiation on the developing brain.^{10,12,13} There is no agreement on a chemotherapeutic protocol.¹⁴⁻¹⁶ Chemotherapy can result in a partial or complete response to treatment, but there is no evidence that it increases the survival rate.⁴ Additionally, drug resistance is common.^{4,9}

Side effects of chemotherapeutic agents are often dose-dependent. The most serious side effects are hematologic. Among the reported visual/ocular side effects of systemic cancer treatments are: blurred vision, color vision defects, lid anomalies, dry eye, conjunctivitis, uveitis, cataract, retinopathy, optic nerve disorders, cranial nerve palsies, fibrosis of the extraocular muscles, and internuclear ophthalmoplegia. The reader is referred to works by Imperia and Schmid for an overall review.^{17,18}

Corticosteroids are often used in patients as an adjunct to chemotherapeutic agents to treat edema that can be associated with intramedullary tumors.⁸

In older patients, focal radiotherapy to the tumor bed is considered standard of care, although there has not been a randomized trial to compare its efficacy to no radiotherapy.^{4,5,7} There is also no standardization for the optimal dose of radiation.^{4,10} As stated previously, radiotherapy has been reserved for children older than 3 years due to the effects of radiation on the developing brain.⁸ However, more recent studies have included infants less than 36 months of age in radiation treatment groups.¹⁶

Adverse effects of radiation include acute encephalopathy, subacute demyelination, and late radiation encephalopathy. Acute encephalopathy can develop within hours, and symptoms may include: headache, agitation, lethargy, nausea, and vomiting.¹⁹ Subacute demyelination is less common and can occur 1-2 months after brain irradiation. Clinical symptoms include brainstem signs such as ataxia or nystagmus and can resolve spontaneously within 2 months.¹⁹ Late encephalopathy can develop months to years after radiation, and symptoms can include seizures, headaches, hemiparesis, and cognitive dysfunction.^{10,19}

Prognosis:

Approximately 33-50% of patients with ependymoma experience a relapse, and 15% experience tumor progression, both within an average time of 24 months.^{3-5,7} Most recurrences are local and occur within 11-25 months, with 10% recurring beyond 3 years.⁴ In patients who experience a recurrence, survival rates are poor (0-25%).⁷

The age at diagnosis and surgical success have been associated with better survival rates. Factors that have been implicated in the five-year survival rate in some studies include treatment type (chemotherapy or radiation only versus in combination), location of tumor, and histology.^{4,6} Survival rates are measured as event-free survival (EFS) and overall survival (OS). Most authors report that overall survival is better in patients diagnosed over the age of 3.^{5,13} For all patients, the 5-year event-free survival rate ranges from 29-51% and the overall survival rate from 43-65%.^{5,6,16}

Patients in whom gross total resection of the tumor is achieved are considered to have a better prognosis compared with patients who have incomplete resections. Studies have found five-year overall survival rates ranging from 59-80% for totally resected tumors and 32-55% for incompletely resected tumors.^{5,6}

Etoposide

Etoposide is a topoisomerase II inhibitor which inhibits DNA synthesis at the G-2 phase of the cell cycle causing cytotoxicity.^{20,21} It is FDA approved for treatment of small cell carcinoma of the lung and testicular cancer.²⁰ Off-label uses include the treatment of various cancers including bladder,

cervical, ependymoma, leukemia, liver, lymphoma, ovarian, prostate, retinoblastoma, and rhabdomyosarcoma.²⁰ Etoposide is available as an oral or intravenous formulation and is dosed in 3-7 week cycles. Among its reported visual side effects are transient cortical blindness and optic neuritis.²¹ There are no reports in the literature of etoposide being associated with strabismus or extraocular muscle dysfunction.

Etoposide has been studied in pediatric patients with brain tumors including ependymomas, medulloblastomas, and optic nerve and brainstem gliomas.^{7,22-24} One study on 12 children with a recurrent intracranial nondisseminated ependymoma with prior subtotal tumor resection and subsequent radiotherapy found that 50% of patients displayed disease progression, 33% remained stable, and 17% showed improvement.²³ Another study of patients under the age of 11 who were treated with etoposide found a median survival of 7 months with a 2-year progression-free rate of 16.7%.²⁴

Side effects in the studies included alopecia, diarrhea, weight loss, mucositis, anemia, and thrombocytopenia. No ocular side effects were recorded.^{22,24,25}

A review of the literature found one case report of ocular side effects in a patient undergoing treatment with etoposide and carboplatin.²⁶ A 52-year-old man with glioblastoma multiforme received an intracarotid injection of carboplatin and etoposide, after which he developed an orbital myositis and later, an anterior uveitis. The authors could not explain the etiology of the acute inflammation.

Diplopia, ptosis, strabismus, and myasthenia-like syndromes have also been reported in association with chemotherapeutic agents, either as case or database reports.^{17,27,28} In many of the reports, patients were on multiple medications, so it is difficult to isolate a single causative agent. Vincristine, like etoposide, is an anti-neoplastic agent and phase-specific mitotic inhibitor that has been implicated in the development of strabismus, ptosis, lagophthalmos, cranial nerve palsies, corneal hyperesthesia, and internal ophthalmoplegia.²⁹

Differential Diagnoses

Cyclic Esotropia

Cyclic esotropia is a rare form of esotropia with an incidence of 3,000-5,000 strabismic patients.³⁰ Cyclic esotropia is not a type of intermittent esotropia but a unique entity where patients display cycles of esotropia alternating with orthophoria. Unlike intermittent esotropia, which often worsens with fatigue, cyclic esotropia usually improves during the day. Cycles are often 24 or 48 hours but can be longer. In some instances, patients are found to have neurological problems. One report describes a patient with a 34 prism diopter esotropia in the morning who developed orthophoria daily at 1-2 pm. This patient later developed seizures. Another patient presented with a 50 prism diopter esotropia on strabismic days and had a slight esotropia on straight days. This patient was later diagnosed with an astrocytoma in the third ventricle.³⁰

In the case report presented in this paper, although the esotropia varied with the timing of the etoposide cycle, it was variable during the eye exam and was not consistent with a true cyclic esotropia.

Acquired Non-Accommodative Esotropia

Acquired non-accommodative esotropia usually develops in patients older than 1 year of age. In one study, the average age of onset was 3.2 years, and 33% of patients developed the esotropia after a fever, while 6.7% of patients developed the esotropia after seizure. The development of the esotropia in the remaining patients was idiopathic.²

A literature review found a case report of a variable angle of strabismus associated with heroin and methadone use.³¹ In the case described, the patient had a prior history of strabismus surgery for exotropia. The patient's exotropia worsened when using heroin. The authors speculate that there may be causality or that the opiate use may create decompensation of a phoria.

Accommodative Dysfunction

Accommodative dysfunction is well-documented in reports on patients with acquired brain injury.³²⁻³⁴ Suchoff found that almost 10% of patients with acquired brain injury had an accommodative dysfunction.³³ Ciuffreda found that 41% of patients with traumatic brain injury and 12.5% of patients with cerebral vascular accidents had a type of accommodative dysfunction.³⁴ Unlike patients in prior studies, the patient in this case report had multiple traumatic insults to his brain: the tumor and regrowth, multiple surgeries, radiation, and chemotherapy. It is possible that any one of the treatments in isolation, or the combination thereof, could have caused damage to the patient's accommodative system.

Optometric Treatment

As with any patient who presents with a binocular vision problem, treatment should attempt to decrease symptoms and increase function. One difficulty in treating this patient was that he could not receive weekly vision therapy. Another difficulty was that his esotropia was variable over time. For these reasons, treatment focused on decreasing the magnitude of the eye turn and attempting to encourage the patient to use both eyes when possible.

Many vision therapy treatment plans exist for the treatment of strabismus. One treatment plan is outlined by Caloroso and Rouse.³⁵ The first stage of treatment includes providing an optical correction using lenses and prisms. When signs of an accommodative insufficiency exist, whether by near retinoscopy, amplitude of accommodation, or accommodative facility testing, plus lenses are indicated.³⁶ In this case report, accommodation was not assessed on subsequent visits. It is also possible that a lower amount of plus might have been effective in treating the patient's symptoms.

After providing an optical correction, therapy should focus on motilities and establishment of fusion.³⁴ For these

areas, the patient in this case was given activities to work on his oculomotor skills. If the patient is able, active therapy such as vectograms, computer orthoptic programs, and free space work with prisms can be performed to aid with the development of fusion. In cases where the patient is too young, or is unable to perform these activities, work on a patient's motor skills can be performed. With patients who present with esotropia, treatment should look to improve divergence and abduction. For example, patients with a right esotropia should be encouraged to do abduction work to the left – looking left, pointing at a target, touching the target. (Brenda Montecalvo, OD, personal communication April 8, 2013).

In this case report, it is possible that the patient had an esotropia prior to the diagnosis of the ependymoma, but in the absence of amblyopia, infantile strabismus could be ruled out. Although this patient had a complex medical history including radiation and multiple surgeries, there are some indicators that point to etoposide as the cause of the esotropia: the timing of the strabismus coincided with the start of the etoposide therapy; the patient's pediatrician referred the patient for an eye turn after starting etoposide, the patient's mother noted the eye turn after he started the medication, and the parents noted improvement in the magnitude of the strabismus when the patient was off the medication. Unlike the corticosteroid, the etoposide was not taken constantly. Similarly, when the steroid treatment was changed, the esotropia was still present.

It would be helpful to have had records from prior eye examinations, if any were done, to compare the magnitude of the strabismus prior to and subsequent to starting chemotherapy. In hindsight, it would also be helpful to have asked the day of the treatment cycle of etoposide for each of the exam visits. Similarly, the patient could have returned for regular visits at different times of the etoposide cycle, but as the family lived 4 hours away from the clinic, frequent travel was not possible. Video documentation of the strabismus was planned but not completed.

In many cases where a drug is suspected of causing ocular side effects, causality is difficult to determine without the discontinuation of the drug (i.e., rechallenge test). In cases where there are ocular side effects, an alternate drug therapy can be attempted to treat the condition. If an alternate drug is not available and ocular symptoms/signs are still present, prisms or occlusion may provide relief.

A formal challenge test was not performed in this case. Stopping a chemotherapeutic agent for a benefit such as eliminating an eye turn must be weighed against the risks such as tumor regrowth. In this case, with an aggressive tumor and no consensus on the best treatment for ependymoma, the risks of stopping the etoposide would outweigh the benefits.

Additionally, when a patient has a life-threatening tumor, a strabismus might be viewed as a secondary, less serious problem, and treatment may be deferred until the patient is stable. In some cases, the strabismus may remain unnoticed by

other medical providers, and if it is noted may be attributed to the tumor or surgery.

Conclusion

Practitioners should be aware of a possible link between strabismus and etoposide treatment in pediatric patients. Even in cases where patients present with strabismus or amblyopia and the prognosis for survival is poor, the eye care practitioner should work to prevent the development of amblyopia and enable the development of fusion when possible in patients who are able.

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