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Case Report

Diagnostic Challenges Concerning an Optic Glioma in an Infant: A Case Report

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Abstract

Optic gliomas most commonly occur during the first decade of life and are usually associated with neurofibromatosis type 1 (NF1). In rare cases, they may arise sporadically. In this report, we present a case of a pediatric patient with nystagmus who is found to have bilateral optic nerve enlargement and enhancement on imaging. Genetic testing for NF1 is negative, suggesting a differential including central nervous system (CNS) NF1 mosaicism and sporadic optic glioma. The patient underwent multiple diagnostic procedures, and is actively receiving chemotherapy. This case highlights the difficulties and uncertainties in the workup of pediatric optic gliomas.

Keywords: Optic Glioma; Neurofibromatosis type 1 (NF1); Sporadic; Mosaicism

Introduction

Optic gliomas account for two to five percent of intracranial tumors in children [1]. A portion may be confined to the optic nerves, while the majority involve the optic chiasm [2]. Typically, optic gliomas are associated with neurofibromatosis type 1 (NF1), but rare cases exist where these tumors may arise sporadically. This case report features a 14-month-old boy with nystagmus, bilateral optic nerve enlargement and enhancement, and genetic testing negative for NF1.

Case Presentation

A 14-month-old boy born full-term in Peru presented to the ophthalmology clinic for nystagmus in the left eye. His parents first noticed "shimmering" of his left eye at age three months. At five months, he was noted to have nystagmus, torticollis, and head bobbing. At time of presentation, he had two cafe-au-lait spots and two hypopigmented melanocytic lesions. He did not have any neurofibromas or Lisch nodules. Family history was notable for autism in a brother and retinitis pigmentosa in a grandmother.

Exam revealed the ability to fixate and follow with both eyes, full extraocular movements, and normal pupillary exam without a relative afferent pupillary defect. Notably, the left eye exam uncovered intermittent esotropia, shimmering low-amplitude nystagmus, and low-frequency intermittent nystagmus. Fundus exam yielded healthy optic discs with sharp margins bilaterally, without obvious edema or atrophy.

MRI brain and orbits and genetic testing were completed for further workup. Imaging exhibited increased bilateral enlargement and enhancement in the optic nerves; enhancement was more noticeable in the prechiasmatic optic segment on the left side and in the post-chiasmic optic segments on the right side. Genetic testing for NF1 DNA +RNA analysis was negative. No acute intervention was given and observation was recommended. The family of the patient was counseled on close monitoring with a multidisciplinary team including pediatric oncology, pediatric ophthalmology, and neuro-ophthalmology.

Six months after initial presentation, a repeat MRI brain and orbits revealed a slight increase in thickness of the mass-like structure along the right post-chiasmatic optic tract. Interval increase in size of intracranial lesion necessitated further workup. A lumbar puncture was performed to look for mosaicism of MF-1 in the CNS. The CSF results were inconclusive, possibly due to inadequate material circulating in the CSF. In the interim, the patient was found to have new temporal pallor of the optic nerve bilaterally. The case was reviewed by the pediatric neuro-oncology tumor board, and the patient was recommended for tissue biopsy, given slight progression of the tumor on MRI, new temporal pallor of optic nerves, and absence of known diagnosis. Transorbital biopsy showed tiny fragments of dense fibro-collagenous tissue consistent with dural sheath and meningothelial cells. It was negative for evidence of definite neoplasm. It was postulated that the biopsy may have been too superficial to determine glial neoplasm.

Five months after the first biopsy, the patient underwent a supraorbital craniotomy for biopsy of optic nerve tumor. Results revealed minute fragments of optic nerve with increased cellularity and atypical cells compatible with low grade glial neoplasm. Molecular testing was positive for a BRAFV600E mutation. The patient was scheduled to start vinblastine weekly per his oncology team.

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Discussion

Sporadic bilateral optic gliomas are rare [3]. Most pediatric optic gliomas are associated with NF1. In a study of 17 children with optic nerve gliomas, 13 (76%) were associated with NF1, and only four patients had sporadic, isolated optic nerve gliomas [3]. All of the bilateral gliomas in the study by Hamideh et al occurred in patients with NF1. In another study of 42 patients with optic glioma, 19 (45%) were positive for NF1 and 23 (55%) were negative [4]. Sporadic optic gliomas occur at younger age of presentation (median age 2.5 years), are more likely symptomatic upon presentation, and are more likely to extend to the chiasmal or post-chiasmal area [3,5-7]. Patients without NF1 are also noted to have significantly higher risk for endocrine complications such as central hypothyroidism or hypocortisolism; anecdotally, reports of increased intracranial pressure and decreased visual acuity occur in these patients [6,7].

A clinical diagnosis of NF1 in young children is difficult due to lack of signs and symptoms of the syndrome. A reported 46% of patients diagnosed with NF1 later in life did not meet the NIH clinical diagnostic criteria by age of one year, while 97% of NF1 patients eventually met diagnostic criteria by age of eight years [8,9]. While the above patient does not currently meet clinical criteria for NF1, it is possible that further clinical symptoms may present in future visits.

While genetic testing is used to guide diagnosis for NF1, it may be inconclusive in some cases. A small fraction of individuals who do meet clinical criteria for NF1 have a genetic variant that is undetectable by genetic testing [10]. In addition, patients with mosaic NF1 may receive false negative results on genetic testing. Mosaic NF1 occurs when there is a somatic mutation in terminally differentiated cells later in embryonic development. It may present as negative on blood genetic testing, but positive if genetic testing is isolated to the affected tissue [11]. If genetic testing is negative but a high clinical suspicion for optic glioma exists, then biopsy may be performed to confirm diagnosis. In a study of 121 patients with optic glioma, 31 (26%) underwent surgical biopsy [12]. After one year of follow-up, the above patient did have a biopsy confirmed optic glioma. However, based on the testing results, it cannot be concluded if there is an underlying NF1 diagnosis.

Interestingly, the biopsy for the above patient showed a BRAFV600E mutation upon molecular testing. Optic pathway gliomas have been predominantly classified as a subtype of astrocytomas [13]. An estimated 59-62% of patients with sporadic optic gliomas have genetic alterations involving the BRAF gene [13-15]. It is possible that the above patient may have a rare sporadic bilateral optic glioma associated with a BRAFV600E mutation.

Nystagmus is a notable clinical finding that may warrant further imaging. One study report 15% of patients with isolated nystagmus have abnormal intracranial findings on MRI; the most common includes abnormal signal lesions, Chiari I malformations, and optic pathway gliomas [16]. Among optic glioma cases, nystagmus is significantly associated with sporadic optic glioma compared to NF1 [17]. In the preceding case, the patient had presented with shimmering nystagmus, thus more suggestive of sporadic optic glioma rather than NF1 diagnosis. There is a need for more research on patients with sporadic optic gliomas and whether they are diagnosed with NF1 in later years, especially as diagnostic testing becomes more advanced.

When monitoring optic nerve glioma, current guidelines recommend a physical, neurologic, and ophthalmologic exam every 3 months and imaging every 3-6 months in the first year after diagnosis [1]. This screening frequency is eventually spaced to annually. The decision to treat optic glioma is based on clinical symptoms or radiologic signs of progression. The above case presentation follows the guidelines of repeat ophthalmologic examinations at minimum every 3 months.

Management of sporadic optic nerve gliomas is difficult. Sporadic optic gliomas tend to have a worse prognosis and are less responsive to chemotherapy and radiation, with greater numbers of patients requiring surgery to prevent progression [1,3,6,17,18]. Factors associated with poor visual outcomes include younger age at presentation, poorer visual acuity at baseline, involvement of the intraorbital optic nerve, intracranial hypertension requiring surgery, and optic nerve atrophy [5,17,18]. As the aforementioned patient does not have clinical signs of NF1, the case would be considered a sporadic optic glioma. Care should be taken due to the high possibility of an aggressive tumor.

Conclusion

The presence of nystagmus in an infant warrants further workup with imaging, as in this case where bilateral optic glioma was discovered. Optic gliomas are often associated with NF1, however sporadic optic gliomas tend to have poor prognosis. It is imperative to monitor frequently with imaging as surgical intervention may be required in order to prevent progression. Early clinical suspicion can expedite diagnosis and management, improving outcomes for patients.

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