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Evaluation of Neurofibromatosis Type 1 Associated Optic Pathway Gliomas

Nörofibromatozis Tip 1 İlişkili Optik Yol Gliomlarinin Değerlendirilmesi

Özge Vural, Arzu Okur, Faruk Güçlü Pınarlı

Gazi University School of Medicine Department of Pediatrics, Division of Pediatric Hematology and Oncology, Ankara, Turkey

Abstract

Aim: Optic pathway gliomas (OPGs) are low-grade gliomas histologically represented by pilocytic astrocytoma (PA) in 90% of cases, can develop from any part of the visual pathways such as optic nerve, chiasm, optic tract, or optic radiations which frequently involve the hypothalamus. OPGs account for 3–5% of childhood central nervous system (CNS) tumors and about 2% of pediatric glial lesions. OPGs are believed to be the most prevalent intracranial tumor in patients with neurofibromatosis type 1 (NF-1) and can occur in 15–20% of NF-1 cases. The aim of this study is to evaluate the clinical features and treatment response in patients diagnosed with optic glioma and NF-1.

Material and Method: All cases diagnosed with OPG and received treatment in the Pediatric Oncology Department, between January 2015 to January 2021 were retrospectively evaluated. Inclusion criteria include children and adolescents with OPG aged between 0 and 18 years. The medical records (gender, age, tumor entity, tumor location) of patients, as well as their treatment history and magnetic resonance imaging (MRI) scans, were examined. The diagnosis of OPG was made clinically and radiologically by the tumor board. The recommendations of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group were used in the diagnosis and evaluation of treatment response. Patients received intravenous chemotherapy with SIOP LGG 2004 (vincristine- carboplatin) with or without bevacizumab (10 mg/kg, started every 2 weeks), therapy or vinblastine (3 mg/m², weekly).

Results: This study included 27 cases during the study period from January 2015 to January 2021. In this study there were 14 male (51.8 %) and 13 female (48.1 %) patients. The median age was 4.8 (range: 0.5–14.9) years. Biopsy was performed in three patients and the diagnosis was low-grade glioma (pilocytic astrocytoma) for all of them. Chemotherapy was administered to 22 cases in total. Twelve patients received vincristine-carboplatine, 5 patients received vincristine-carboplatin with bevacizumab and 5 patients received vinorelbine. Radiological response was evaluated in all 22 patients at 3 months MRI. No patient had a radiological complete respons, 11 patients (50%) had partial response, 2 patients (9%) presented with a progressive disease, showing an increase in measurements of 35% and 9 patients(40.9%) had stable disease at the 3-month evaluation.

Conclusion: Systemic and visual problems play a significant role to initiate of treatment for pediatric patients with optic gliomas. An essential treatment option for improving symptoms and reducing tumor size is systemic chemotherapy. A crucial therapy option for enhancing vision is bevacizumab for the patients with NF-associated OPG.

Keywords: Pediatric cancers, optic pathway gliomas, bevacizumab

Öz

Amaç: Optik yol gliomaları (OPG'ler), vakaların %90'ında histolojik olarak pilositik astrositom (PA) olan düşük dereceli gliomalardır ve optik sinir, kiazma gibi görme yollarının herhangi bir kısmından hipotalamusa kadar uzanım göstererek gelişebilirler. OPG'ler çocukluk çağı merkezi sinir sistemi (CNS) tümörlerinin %3-5'ini ve pediatrik glial lezyonların yaklaşık %2'sini oluşturur. OPG'lerin, nörofibromatozis tip 1 (NF-1) hastalarında en yaygın intrakranyal tümör olduğu düşünülmektedir ve NF-1 vakalarının %15-20'sinde ortaya çıkabilmektedir. Bu çalışmanın amacı optik gliom ve NF-1 tanısı alan hastaların klinik özelliklerini ve tedavi yanıtını değerlendirmektir.

Gereç ve Yöntem: Ocak 2015 ile Ocak 2021 tarihleri arasında Çocuk Onkoloji Bölümü'nde OPG tanısı alan ve tedavi gören tüm olgular retrospektif olarak değerlendirildi. Dahil edilme kriterleri arasında OPG'li 0 ila 18 yaş arası çocuklar ve ergenler yer almaktadır. Hastaların tıbbi kayıtları (cinsiyet, yaş, tümör varlığı, tümörün yerleşim yeri), tedavi öyküleri ve manyetik rezonans görüntüleme (MRG) tetkikleri incelendi. OPG tanısı tümör konseyi tarafından klinik ve radyolojik olarak konuldu. Tedavi yanıtının tanılanması ve değerlendirilmesinde Pediatrik Nöro-Onkolojide Yanıt Değerlendirmesi (RAPNO) çalışma grubunun önerilerinden yararlanıldı. Hastalar bevacizumab (10 mg/kg, her 2 haftada bir başlanır) ile birlikte veya bevcizumab olmadan SIOP LGG 2004 (vinkristin-karboplatin) ile intravenöz kemoterapi veya vinblastin (haftalık 3 mg/m²) aldı.

Bulgular: Bu çalışmaya Ocak 2015 ile Ocak 2021 arasındaki çalışma döneminde 14'ü erkek (%51,8) ve 13'ü kız (%48,1) toplam 27 vaka dahil edildi. Ortanca yaş 4,8 (aralık: 0,5-14,9) yıldı. Üç hastaya biyopsi yapıldı ve hepsine düşük dereceli glioma (pilositik astrositom) tanısı konuldu. Toplam 22 olguya kemoterapi uygulandı. On iki hastaya vinkristin-karboplatin, 5 hastaya bevacizumab ile birlikte vinkristin-karboplatin ve 5 hastaya vinorelbin verildi. 22 hastanın tamamında 3. aydaki MRG'de radyolojik yanıt değerlendirildi. Hiçbir hastada radyolojik tam yanıt görülmedi, 11 hastada (%50) kısmi yanıt, 2 hastada (%9) ilerleyici, 9 hastada (%40.9) stabil hastalık görüldü.

Sonuç: Optik gliomlu pediatrik hastalarda tedavi seçiminde sistemik ve oküler bulgular önemlidir. Sistemik kemoterapi oküler bulguların iyileştirilmesinde ve tümör boyutunun küçültülmesinde önemli bir seçenektir. Bevacizumab tedavisi tümör boyutunu küçültmese de görsel bulguları iyileştirmektedir.

Anahtar Kelimeler: Pediatrik kanserler, optik yol gliomları, bevacizumab

Corresponding *(İletişim)*: Özge VURAL, Gazi University School of Medicine Department of Pediatrics, Division of Pediatric Hematology and Oncology, Ankara, Turkey
E-mail *(E-posta)*: drozgevural@yahoo.com
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INTRODUCTION

Optic pathway gliomas (OPGs) are low-grade gliomas histologically represented by pilocytic astrocytoma (PA) in 90% of cases, can develop from any part of the visual pathways such as optic nerve, chiasm, optic tract, or optic radiations which frequently involve the hypothalamus.[1] OPGs account for 3–5% of childhood central nervous system (CNS) tumors and about 2% of pediatric glial lesions.[2] OPGs are believed to be the most prevalent intracranial tumor in patients with neurofibromatosis type 1 (NF-1) and can occur in 15–20% of NF-1 cases. Some chromosomal abnormalities, notably deletion of chromosome 17q and neurofibromin (in NF-1 patients), have been regarded as the underlying etiology of this tumor.

The majority of patients with symptomatic optic tract glioma are diagnosed before the age of six years. Children with OPGs are frequently diagnosed after visual deficits are noted; other symptoms at presentation include proptosis or symptoms of the hypothalamic syndrome, correlating with the anatomic tumour location and side. Clinical symptoms differ according to the location of the lesion.[3] Although patients may be asymptomatic, the most commonly described symptom is vision loss, regardless of tumor location. The relationship between tumor size and visual symptoms has not been well established. Tumors located in the anterior part of the optic tract may present with unilateral vision loss, strabismus and/or proptosis. Proptosis is a more common symptom in patients with NF1. A tumor located in the optic chiasm may present with loss of vision, nystagmus, and decreased visual acuity.[1] Hydrocephalus, diencephalic syndrome and multiple endocrine disorders can be detected in lesions in the hypothalamic region.[4]

The visual assessment is crucial since preservation of vision is a critical goal of the management of OPG. Imaging is crucial in the diagnosis and management of OPG together with ocular evaluation. Following a clinical examination and magnetic resonance imaging (MRI), the diagnosis is typically made. A biopsy is not required when a tumor exhibits the typical clinical traits and imaging findings in NF1 patients.

There is no consensus on the best way to handle pediatric OPG; the choice of treatment relies on the patient's age, NF1 status, tumor size, tumor location, and, most importantly, how the tumor affects neurological and visual abilities, leading to functional deficits.

The choice of treatment (wait and see, surgery, radiotherapy, chemotherapy or possibly targeted therapy) is one of the most challenging and controversial aspects of the disease, although current consensus is to treat children with evidence of visual or neurological deterioration.

A variety of different drug regimens have shown efficacy, achieving 5-year progression free survival (PFS) depending on the regimen: weekly vinblastine with a PFS of 53.2%;[5] SIOP LGG 2004 (vincristine- carboplatine) with a PFS of 46%.[6] Among new therapies, bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF).[7] Brain tumors and among-all low grade gliomas have been shown to express high levels of VEGF.[8] The expected mechanisms of action of Bevacizumab are tumor size stabilization/reduction and vision sparing.

The aim of this study is to evaluate the clinical features and treatment response in patients diagnosed with optic gloma and NF-1.

MATERIAL AND METHOD

The study was approved by Gazi University Clinical Researches Ethics Committee (Date: 24.01.2022, Decision no: 49). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

All cases diagnosed with OPG and received treatment in the Pediatric Oncology Department, between January 2015 to January 2021 were retrospectively evaluated. Inclusion criteria include children and adolescents with OPG aged between 0 and 18 years. Patients who had their initial treatment at other centers and were referred to us for further management were excluded from the study.

The medical records (gender, age, tumor entity, tumor location) of patients, as well as their treatment history and MRI scans, were examined. The diagnosis of OPG was made clinically and radiologically by the tumor board. In addition, we removed all identifiers from our data after the analyses were completed to protect patient privacy.

The recommendations of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group were used in the diagnosis and evaluation of treatment response.

The width, transverse, and length measurements obtained from MRI images were used to evaluate the tumor response criteria. A complete response (CR) was defined as no evidence of disease (enhancing or nonenhancing, measurable or non-measurable) maintained for ≥8 weeks; no new lesions, whereas a partial response (PR) was defined as ≥25% decrease (compared with baseline) in the 2D product of the largest perpendicular diameters (using T2-weighted or FLAIR sequences) maintained for ≥8 weeks. Progressive disease (PD) was defined as ≥25% increase (compared with smallest measurement at any timepoint from trial baseline) in the 2D product of the perpendicular diameters (using T2-weighted or FLAIR sequences), whereas stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The term "objective response" (OR) was used to describe all patients who had either a PR or a CR. The disease control rate (DCR) was defined as CR + PR + SD, whereas the response rate (RR) was defined as CR + PR.[9]

Clinical evaluation by trained pediatric ophthalmologists was performed at the same time as the radiological evaluation, with assessment of visual acuity, as well as the visual field (VF) whenever feasible.

Biopsy was performed on large masses extending beyond the optic nerve.

In case of tumor progression and visual deterioration, treatment was started.

Patients received intravenous chemotherapy with SIOP LGG 2004 (vincristine- carboplatin) (6) with or without bevacizumab (10 mg/kg, started every 2 weeks), therapy or vinblastine (3 mg/m², weekly).

The criterias of wait and see option are stable mass on MRI and stable vision loss.

Statistics

Calculations were made using the Statistical Package for Social Studies (SPSS, version 18). Descriptive statistical methods were used.

RESULTS

This study included 27 cases during the study period from January 2015 to January 2021. Patients' characteristics are summarized in **Table 1**. In radiological evaluation hamartomas were detected in 11 (44.4%) patients. Epilepsy was identified after further evaluation in a patient.

Biopsy was performed in three patinets and the diagnosis were low grade glioma (pilocytic astrocytoma) for all of them.

Table 1. Patients' characteristics

Median age at diagnosis (range)	4.8 years (0.5–14.9 y)
Female/Male	13/14
Family History	19(70.4%)
Café-au-lait macules	12 (44.4%)
Freckling in the axillary region	8(29.6%)
Neurofibromas	3(11.1%)
Plexiform neurofibromas	1(3.7%)
Lisch nodules	4(14.8%)
Bone abnormalities	1(3.7%)

Five patients were asymptomatic and choice of treatment was wait and see.

Chemotherapy was administered to 22 cases in total. Twelve patients received vincristine-carboplatin, 5 patients received vincristine-carboplatin with bevacizumab and 5 patients received vinorelbine.

The median follow up time was 2.7 (0.8-4.3) years.

Radiological response was evaluated in all 22 patients at 3 months MRI. No patient had a radiological CR, 11 patients (50%) had partial response, 2 patients (9%) presented with a progressive disease, showing an increase in measurements of 35% and 9 patients (40.9%) had stable disease at the 3-month evaluation. Radiological response is summarized in **Table 2**.

Table 2. Objective radiological responses according to RAPNO criteria at 3-month MRI

Radiological Response	3-Month Evaluation
Complete response	0 (0%)
Partial response	11(50%)
Stable disease	9 (40.9%)
Progressive disease	2 (9%)

RAPNO: Response Assessment in Pediatric Neuro-Oncology, MRI: Magnetic Resonance Imaging.

Visual assessment for visual acuity was available for 22 patients. Five patients (18.5%) were not evaluated due to low age and cognitive status. Objective clinical/ophthalmological response to the therapy was the following: steady state in twelve patients (54.5%), significant improvement in six patients (27.2%), and significant worsening in four patients (18.1%).

Radiologic response and visual response were not compatible with each other in all patients, but could not be evaluated because of small the number of the patients.

Five patients received bevacizumab combination therapy and all ofthem had stable disease at the 3-month evaluation. When the ophthalmologic response was evaluated, significant improvement was observed in 3 patients and steady state was observed in 2 patients.

While two patients were being evaluated for malnutrition, they were diagnosed with OPG in MRI. Diencephalic syndrome was observed in these two patients. They were diagnosed at 12 and 18 months of age respectively. Both of them received vincristin, carboplatin with bevacizumab and symptoms were improved with treatment.

There was one patient under the age of 12 months. An optic glioma was detected in the MRI while the 6-month-old girl was being evaluated for febrile seizure. In the patient's three-month follow-up, there was no radiological progression noted.

DISCUSSION

OPGs make up for 3-5% of all pediatric CNS malignancies and are the most common intrinsic optic nerve tumors, but the overall results of any therapeutic approach whether visually or radiologically have not yet been studied well. Children with NF-1 are more likely to develop these tumors, and they do so more frequently in the first ten years of life.[10] OPGs are typically low-grade tumors, but they might behave aggressively, making it difficult to use some therapeutic methods. Age less than one year is thought to be a significant unfavorable factor for mortality in OPG patients.[11] While some studies did not find a significant difference,[12] some studies showed that NF-1 is a good predictive factor. The presence of a diencephalic syndrome at the time of diagnosis, especially when it is linked to leptomeningeal dissemination, is believed to be a significant prognostic factor.[4] In our study the median age was 4.8 (range: 0.5–14.9) years.

Some retrospective evaluations suggest that some children with OPG might not require active intervention.[13] In our study five patients did not receive any chemotherapy, radiotherapy or surgery. We decided for the wait and see approach to treatment, and none of these five patients showed signs of deterioration.

Chemotherapy has never been proven to be totally effective in preventing vision loss. Chemotherapy that is administered systemically may arrest the decline of visual acuity and stabilize vision. Nearly one-third of children who got chemotherapy for NF-associated OPG showed some improvement in their vision. The combination of carboplatin and vincristine regimen and the weekly vinblastine treatment are two of the most often utilized chemotherapy regimens.[5] According to meta analysis which is based on the available data, a favorable radiological outcome was achieved in 72% (95%CI 64–78) of OPG patients who underwent chemotherapy, while a favorable visual outcome was attained in 75% (95%CI 67–81) patients. Overall, chemotherapy is effective at stopping the tumor's progression and vision loss in OPGs.[14] In our study Bevacizumab-based therapies have been used successfully in children with low grade gliomas.[15] The visual threat is still the major reason to use bevacizumab, and it is comforting to see almost all patients achieve stability. After the treatment, a decrease in contrast enhancement and a decrease in the cystic part are observed in the majority of patients.[16] Patients who received bevacizumab in our study either had stable disease or improved clinical and ophthalmological outcomes; none of the patients' diseases worsened.

Gastrointestinal dysfunction, leukopenia and hypertension were the toxic side effects of bevacizumab treatment with the highest incidence in pediatric population. No side effects related to bevacizumab were observed in the study group.

The uncommon symptom complex known as diencephalic syndrome (DS) is connected to malignancies in the hypothalamus and is most frequently observed in children with optic pathway/hypothalamic glioma.[17] Weightloss leading to malnutrition can be seen in DS.[18] In a study consist of 520 patients with low grade gliomas from Toronto, 9 patients with DS were treated with chemotherapy with good treatment response but 7 of them progressed and needed multiple lines of treatment.[19] Two of these 9 patients with DS had NF1 and were treated with chemotherapy.[4] Initial chemotherapy with carboplatin and vincristine was used in NF1-associated OPHG presenting with DS patients.[20] Also, targeted treatment with bevacizumab led to treatment response after progression in some studies.[21] In our study two patients who were being evaluated for malnutrition, were diagnosed with OPG in MRI. Diencephalic syndrome was observed in these two patients. Both of them received vincristin, carboplatin with bevacizumab and symptoms were improved with treatment.

The limitations of the study were that it was a single-center, retrospective study and had a small number of patients.

CONCLUSION

Systemic and visual problems play a significant role for initiating treatment for pediatric patients with optic gliomas. An essential treatment option for improving symptoms and reducing tumor size is systemic chemotherapy. A crucial therapy option for enhancing vision is bevacizumab for the patients with NF-associated OPG.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Gazi University Clinical Researches Ethics Committee (Date: 24.01.2022, Decision no: 49).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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