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CLINICAL STUDY

# Functional changes after treatment of optic pathway paediatric low-grade gliomas

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## Abstract

*Objective* **To evaluate the functional changes after treatment of paediatric optic pathway gliomas (OPGs).**

*Methods* **All patients with monofocal OPG seen from January 2004 to January 2011 were included. Best corrected visual acuity (BCVA, LogMAR), contrast sensitivity (Hiding-Heidi low-contrast 'face' test (HH) and Pelli – Robson (PR) contrast sensitivity test), and the Color Test (Ishihara plate) were obtained.**

*Results* **Twenty-one patients (10 boys and 11 girls with a mean age of 5.5 ± 4.4 years at diagnosis) were included in the study. Neurofibromatosis was present in four cases. Eighteen patients (85.7%) were treated with initial surgery and three patients (14.3%) with initial chemotherapy. BCVA was 0.67 ± 0.8 LogMAR at baseline and 0.62 ± 0.9 LogMAR at last visit ($P = 0.41$). The Color test was not significantly changed at last visit ($P = 0.62$). Contrast sensitivity with the HH test was 9.1 ± 11.1% at baseline and 3.8 ± 6.4% at last visit ($P = 0.03$). Contrast sensitivity with PR chart was 1.33 ± 0.9log at baseline and 1.05 ± 0.7 log at last visit ($P = 0.005$). A reduction in contrast sensitivity at both tests was significantly greater in patients who relapsed than in patients who did not relapse ($P = 0.001$).**

*Conclusion* **After the treatment of paediatric optic pathway low-grade gliomas, a reduction in contrast sensitivity during follow-up was observed and may be correlated with tumour relapses.**


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*Keywords:* Low-grade gliomas; astrocytoma; contrast sensitivity; relapse

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## Introduction

Optic pathway gliomas (OPGs) represent about 3–5% of brain tumours in children.[1,2] They affect young children more than adolescents or adults and are important in the differential diagnosis of vision loss in children. Approximately 65% of OPGs are detected in children younger than 5 years of age; most of the remaining cases are diagnosed before 15 years of age.[3–5] They are also associated with neurofibromatosis type 1 (NF1), a relatively common genetic condition with an incidence of 1 : 3000 births.[6,7] The tumours are low-grade pilocytic astrocytomas but show a highly variable growth pattern ranging from indolent to rapidly progressive.[8] The management of the OPGs remains a highly controversial topic among neuro-ophthalmologists.[9] Although these tumours are typically low-grade gliomas (LGGs), decision making is difficult because of the highly variable clinical course, and spontaneous regression was also reported.[10,11]

## Methods

A total of 67 children visited for OPG could be identified in the data pool of the University Federico II and the AORN Santobono-Pausilipon of Naples from January 2004 to January 2011. IRB approval was obtained and the parents of all eligible patients were contacted and gave their informed consent to obtain the data. Inclusion criterion was the presence of monofocal OPGs. Forty-six patients had to be excluded for various reasons: histology ruled out an LGG, insufficient postoperative imaging, presence of dysembryoplastic neuroepithelial tumours at diagnosis, and presence of multifocal or disseminated tumour. The WHO classification for grade I and II gliomas and mixed neuronal–glial tumours was used.[12] The anatomical review of imaging reports (RF, AP) was performed blind to clinical details. Age at diagnosis, neurofibromatosis, sex, extent of

resection, time from diagnosis to the start of therapy, histology, and location were analysed.

The diagnosis was dated when confirmatory pathologic tissue was obtained. For patients without tissue confirmation, the date of diagnosis was the date on which the tumour was first detected on imaging studies. In patients, for whom surgical resection had been attempted, the median interval from radiographic diagnosis to surgical procedure was 10 days (interquartile range, 3–21.2 days).

The assignment of primary therapy (observation, surgical resection, chemotherapy or radiotherapy) was determined by the original intent of the treating physician. Surgery was considered the primary therapy either in cases where it seemed anatomically feasible to achieve a complete resection or in situations where a subtotal resection would provide significant symptomatic relief. The extent of resection was defined by the neurosurgeon in the operative and follow-up notes. Several chemotherapy regimens were used, all of which are considered equally effective in LGGs,[13] but first-line chemotherapy was most often a regimen of carboplatin and vincristine. Radiation therapy (RT) was reserved for older children without NF1. RT was classified as adjuvant if administered before evidence of progression after primary surgical therapy (median, 37 days postoperatively; range, 18–106 days). Salvage RT required radiographic evidence of progression and was administered a median of 19.3 months postoperatively (range, 1.4–57.2 months). RT was delivered using computed tomography- or resonance imaging (MRI)-based planning and used megavoltage linear accelerators with fraction sizes of 1.8–2 Gy per day.

Clinical–neurological assessment and neuroimaging (either contrast-enhanced computed tomography or MRI) were qualified as follow-up. Following the start of chemotherapy, follow-up visits were recommended at week 12, 24, 36, 48, and after week 53. During primary observation as well as after the completion of radiotherapy and chemotherapy, radioimaging was performed every 3 months during the first year and with gradually increasing intervals thereafter. Clinical and ophthalmologic assessments were recommended with a similar time frame.

At baseline and at each visit, best corrected visual acuity (BCVA, LogMAR), contrast sensitivity (Hiding-Heidi low-contrast 'face' test (HH) in patients younger than 3 years and Pelli – Robson (PR) contrast sensitivity test in patients older than 3 years) and the Color Test (Ishihara plate) were obtained.

Statistical analyses were performed with STATA 9.0 (Stata Corp., College Station, TX). Multivariable analyses by Cox regression model were performed for progression-free survival following the start of therapy. Survival curves were calculated using the Kaplan–Meier method. The significance level for all analyses was set at 5%.

## Results

Twenty-one patients (10 boys and 11 girls with a mean age of 5.5 ± 4.4 years at diagnosis) were included in the study. Neurofibromatosis was present in four cases. The most common tumour locations were optic pathway/hypothalamus ($n = 8$), midbrain/tectal plate ($n = 6$), brain stem ($n = 4$), and cerebellum ($n = 3$). The most common pathological condition was pilocytic astrocytoma ($n = 12$, 57.1%; Table 1). Age at diagnosis was similar in patients with pilocytic astrocytoma to that in patients with different diagnosis ($P = 0.38$).

Eighteen patients (85.7%) were treated with initial surgery and three patients (14.3%) with initial chemotherapy. Of the patients who underwent initial surgery, extensive surgery was performed in 13/18 cases (72.2%), subtotal surgery in 4/18 cases (22.2%), and biopsy in 1/18 cases (5.5%). Reflecting treatment approach, mean ages were 5.8 ± 4.6 (range, 1.2–17) years for those treated with initial surgery and 3.6 ± 2.9 (range, 0.5–6.3) years for those treated with initial chemotherapy.

After surgery, adjuvant chemotherapy alone was administered in 7/18 cases (38.9%), combined adjuvant radio-chemotherapy was administered in 2/18 cases (11.1%), and adjuvant RT alone was administered in 2/18 cases (11.1%).

The mean follow-up after first treatment was 46.5 ± 25.5 (3–84) months. Overall survival was 100%. Eight out of 18 patients (44.0%) treated with initial surgery aged 3.5 ± 2.0 years and relapsed after 25.3 ± 19.4 months (Figure 1). Overall relapse-free survival for the 18 patients treated with initial surgery was 37.2 ± 26.8 months. The mean age of patients who did not relapse was 6.7 ± 5.1 years. Age was significantly lower in patients who relapsed when compared with patients who did not relapse ($P = 0.01$). The three patients treated with initial chemotherapy did not relapse after 30.3 ± 25 months of follow-up (Figure 1).

BCVA was 0.67 ± 0.8 LogMAR at baseline and 0.62 ± 0.9 LogMAR at last visit ($P = 0.41$; Table 2). The Color test was not significantly changed at last visit ($P = 0.62$). Contrast sensitivity with the HH test was 9.1 ± 11.1% at baseline and 3.8 ± 6.4% at last visit ($P = 0.03$). Contrast sensitivity with the PR chart was 1.33 ± 0.9log at baseline and 1.05 ± 0.7log at last visit ($P = 0.005$). A reduction in contrast sensitivity at both HH test and PR chart was significantly greater in patients who relapsed ( − 3.75% and − 0.56log, respectively) than in patients who did not relapse ( − 0.84% and − 0.13log, respectively) ($P = 0.001$). Of eight patients (11 eyes) with a BCVA 0 LogMAR at

**Table 1** Pathology, site, treatment, and relapses in 21 paediatric patients with low-grade glioma

| *No.* | *Sex* | *Age at diagnosis (years)* | *FU from diagnosis (months)* | *Histology* | *Localization* | *Relapses (Y/N)* | *Time to relapse (months)* | *Neuro-fibromatosis* | *Surgery (yes/no)* | *Treatment strategy* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 1.5 | 39 | A WHO 1 | Brain stem | Y | 5 | N | Y | Surgery |
| 2 | M | 9.7 | 12 | PA WHO 1 | Chiasm | N | — | N | Y | Surgery |
| 3 | F | 6 | 72 | PA WHO 1 | Hypothalamus | N | — | N | Y | Surgery + CT |
| 4 | M | 2.5 | 17 | PA WHO 1 | Cerebellum | N | — | N | Y | Surgery |
| 5 | F | 3 | 28 | A WHO 1 | Hypothalamus | Y | 36 | N | Y | Surgery + RT |
| 6 | M | 15 | 42 | PA WHO 1 | Hypothalamus | N | — | N | Y | Surgery |
| 7 | F | 8 | 39 | A WHO 1 | Thalamus | N | — | N | Y | Surgery + CT |
| 8 | M | 4.6 | 68 | PA WHO 1 | 3rd ventricle | Y | 24 | N | Y | Surgery + RT + CT |
| 9 | F | 1.2 | 33 | PA WHO 1 | Optic nerve | N | — | Y | Y | Surgery + CT |
| 10 | F | 2.4 | 72 | A WHO 1 | Brain stem | Y | 64 | N | Y | Surgery + CT |
| 11 | M | 2 | 84 | PA WHO 1 | Optic pathway | N | — | N | Y | Surgery + CT |
| 12 | F | 6.3 | 3 | A WHO 1 | Chiasm | N | — | Y | N | CT |
| 13 | M | 2.8 | 18 | PA WHO 1 | Third ventricle | Y | 3 | N | Y | Surgery + CT |
| 14 | F | 17 | 12 | PMA WHO 1 | Brain stem | N | — | N | Y | Surgery + RT |
| 15 | M | 4 | 52 | A WHO 1 | Thalamus | N | — | N | N | CT |
| 16 | F | 0.5 | 36 | A WHO 1 | Chiasm | N | — | Y | N | CT |
| 17 | F | 4 | 72 | PA WHO 1 | Thalamus | Y | 24 | N | Y | Surgery + CT |
| 18 | M | 10 | 72 | PA WHO 1 | Thalamus | N | — | N | Y | Surgery |
| 19 | M | 2 | 72 | A WHO 1 | Brain stem | Y | 16 | Y | Y | Surgery |
| 20 | F | 8 | 36 | PA WHO 1 | Cerebellum | Y | 31 | N | Y | Surgery |
| 21 | M | 5.5 | 84 | GG WHO! | Cerebellum | N | — | N | Y | Surgery + RT + CT |

Abbreviations: PA, pilocytic astrocytoma; A, astrocytoma; GG, ganglioglioma; WHO, world health organization classification; CT, chemotherapy; RT, radiotherapy.

baseline, local relapse occurred in three cases. Of them, in no case BCVA reduction during follow-up was observed ($P = 0.72$), whereas contrast sensitivity decreased from 5 to 1.25% in one case and by $-1 \pm 1.1$log at PR chart at last visit in the remaining cases ($P = 0.01$).

## Discussion

To our knowledge, this is the first evaluation of changes of contrast sensitivity according to relapse of disease in children with optic LGG. According to our data, a significantly greater reduction of contrast sensitivity was present in patients who relapsed during follow-up, whereas visual acuity and colour test remained unchanged during the follow-up. Furthermore, in patients with normal visual acuity at diagnosis, contrast sensitivity showed to be a more sensitive indicator of optic compression than visual acuity during follow-up. Avery *et al*[14] showed that 56% of patients with visual acuity of 20/40 or better had a reduced retinal nerve fibre layer on optical coherence tomography. Some children with decreased RNFL thickness had normal high-contrast VA but abnormal visual fields. Interestingly, other children were found to have normal VA and normal visual fields, despite a significantly decreased RNFL. The authors suggested that RNFL thickness is a rapid, noninvasive, objective quantitative measure of visual pathway integrity in children with OPGs. Kelly *et al*[15] showed that visual evoked potentials (VEPs) were a more sensitive indicator of optic pathway damage than visual acuity or optic nerve appearance. The authors suggested to apply VEP in the management of children with OPG to assess the child with mildly or moderately reduced acuity in whom the VEP corroborates progressive visual pathway damage. Furthermore, the same study showed that initial visual acuity and tumour

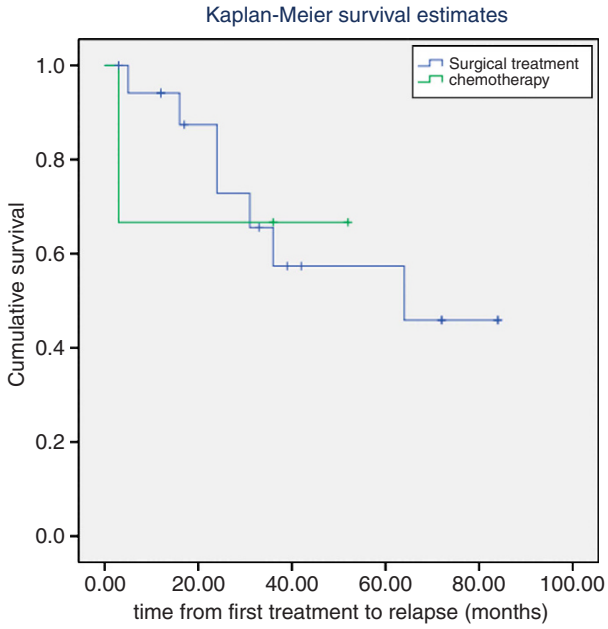


**Figure 1** A Kaplan–Mayer curve showing relapse-free survival in 21 paediatric patients with monofocal optic pathway gliomas according to initial treatment.

**Table 2** Clinical characteristics in 21 paediatric patients with low-grade glioma

| *No.* | *BCVA LogMAR RE pre* | *BCVA LogMAR LE pre* | *BCVA LogMAR RE post* | *BCVA LogMAR LE post* | *Hiding-Heidi test (%) RE pre* | *Hiding-Heidi test (%) LE pre* | *Hiding-Heidi test (%) RE post* | *Hiding-Heidi test (%) LE post* | *Pelli – Robson contrast sensitivity test (log units) RE pre* | *Pelli – Robson contrast sensitivity test (log units) LE pre* | *Pelli – Robson contrast sensitivity test (log units) RE post* | *Pelli – Robson contrast sensitivity test (log units) LE post* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.2 | 0.4 | 0.1 | 0.1 | 1.25 | 1.25 | 1.25 | 1.25 | — | — | — | — |
| 2 | 0.2 | 0 | 0.1 | 0 | — | — | — | — | 0.9 | 2.1 | 0.9 | 2.1 |
| 3 | 0 | 0 | 0 | 0 | — | — | — | — | 2.1 | 2.1 | 2.1 | 2.1 |
| 4 | 1 | 1 | 0 | 0.1 | 25 | 1.25 | 1.25 | 1.25 | — | — | — | — |
| 5 | 0 | 0 | 0 | 0 | 5 | 5 | 1.25 | 1.25 | — | — | — | — |
| 6 | 0 | 0 | 0 | 0 | — | — | — | — | 2.1 | 2.1 | 1.2 | 1.2 |
| 7 | 0.2 | 2.3 | 0 | 2.3 | — | — | — | — | 0.8 | 0 | 2 | 0 |
| 8 | 2.3 | 0 | 2.3 | 0 | — | — | — | — | 0 | 2.1 | 0 | 1.2 |
| 9 | 1.3 | 1.3 | 1 | 1.1 | 25 | 25 | 1.25 | 25 | — | — | — | — |
| 10 | 1.1 | 1.1 | 2.3 | 2 | 25 | 25 | 10 | 10 | — | — | — | — |
| 11 | 0.1 | 2.3 | 0 | 2.3 | 1.25 | — | 1.25 | — | 2 | 0 | 2.1 | 0 |
| 12 | 0.1 | 0.1 | 0.1 | 0.1 | — | — | — | — | 1.9 | 2 | 0,9 | 0,9 |
| 13 | 0.1 | 0.1 | 0 | 0.1 | 1.25 | 1.25 | 1.25 | 1.25 | — | — | — | — |
| 14 | 2.1 | 0 | 2.1 | 0 | — | — | — | — | 0 | 2.1 | 0 | 2.1 |
| 15 | 0.3 | 0.3 | 0.1 | 0.2 | — | — | — | — | 0.75 | 0.75 | 0,9 | 1 |
| 16 | 1.1 | 2.3 | 0.5 | 2.3 | 1.25 | — | 1.25 | — | — | — | — | — |
| 17 | 0.1 | 0.1 | 0.1 | 0.1 | — | — | — | — | 2 | 2 | 2 | 2 |
| 18 | 2.3 | 0 | 2.3 | 0 | — | — | — | — | 0 | 2.1 | 0 | 0,9 |
| 19 | 1 | 1 | 0.3 | 1.1 | 1.25 | 1.25 | 1.25 | 1.25 | — | — | — | — |
| 20 | 0 | 0 | 0 | 0 | — | — | — | — | 2.1 | 2.1 | 1.2 | 0.9 |
| 21 | 2.3 | 0.4 | 2.3 | 1 | — | — | — | — | 0 | 0.5 | 0 | 0.15 |

Abbreviations: BCVA, best corrected visual acuity, LogMAR; LE, left eye; RE, right eye.

volume predicted visual acuity at last examination. Larger tumour volume at presentation predicted long-term progressive visual decline, which likely reflects the severity of preexisting visual pathway damage. Although MRI may be used to make the diagnosis of OPGs, radiographic characteristics have not been shown to correlate with the likelihood of tumour progression.[9]

It has been shown that contrast sensitivity is reduced at low spatial frequencies in patients with optic nerve compression.[16,17] In patients with LGG and normal visual acuity at diagnosis, contrast sensitivity seems to be a more sensitive indicator of tumour progression than visual acuity.

Most optic gliomas are low-grade astrocytomas. Most of the patients in our study had pilomyxoid astrocytomas and 85.7% underwent surgical excision (extensive or subtotal) as first treatment. Of them, 44% relapsed. Chemotherapy was used as first treatment in 3/21 cases (14.2%) and did not lead to relapse. Although chemotherapy is nowadays the mainstay of treatment when indicated,[18] our study was started in 2004 and surgery was the most used treatment for OPG in our clinic until 2009. Previous studies report 16.9% of relapse after surgical removal and 11% of relapse after nonsurgical treatment,[18, 19] According to our results, surgical and nonsurgical treatment modalities of LGG in paediatric patients do not seem sufficient to limit disease progression.

In conclusion, optic LGGs in childhood carry a good prognosis for overall survival, although relapses are frequent. A reduction in contrast sensitivity during follow-up could represent a noninvasive method to detect tumour relapse. A prospective longitudinal study is planned to assess these data.

**Summary**

**What was known before**

- Optic pathway gliomas represent about 3–5% of brain tumours in children. Management is difficult due to the highly variable clinical course.

**What this study adds**

- Optic low-grade gliomas in childhood carry a good prognosis for overall survival, although relapses are frequent. A reduction of contrast sensitivity during follow-up could represent a noninvasive method to detect tumour relapse.

## Conflict of interest

The authors declare no conflict of interest.

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