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Assessment of visual function in patients with posterior fossa tumours. A retrospective study

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ABSTRACT

Introduction. Posterior fossa tumours (PFTs) frequently present with ophthalmic complaints. The literature is mainly focused on PFTs affecting the pediatric age group, and the post-treatment visual outcomes (VOs) are scarcely reported.

Objective. To evaluate the VOs at 6 months following the index surgery in patients with PFTs.

Materials and methods. This retrospective study involved 50 patients of all age groups who underwent surgical resection of PFTs in the Department of Neurosurgery. The patients with PFTs, except those with low-grade tumours, received concurrent chemo-radiotherapy. Pre- and postoperative (6 months after the index surgery) ophthalmic examinations were done and compared. VOs included colour vision, night vision, visual acuity (VA), pupillary function (size, reactivity), papilledema grade, splinter haemorrhage, retinal venous dilatation, strabismus (esotropia and hypertropia), and nystagmus.

Results. The patients were mainly aged 1–10 years (22%) with slight female predominance (52%). The most common PFTs were brainstem glioma and pilocytic astrocytoma (each 18%). At 6 months, there was no significant change in colour and night vision, pupil size and reactivity, splinter haemorrhage, and hypertropia (all p-values>0.05). A significantly lesser proportion of patients had moderate VA (p-value=0.013), retinal venous dilatation (p-value=0.001), and grade 1 (p-value=0.005) as well as grade 4 papilledema (p-value=0.041). Moreover, a significantly greater proportion of patients had grade 0 papilledema (p-value<0.0001). While the incidence of nystagmus and esotropia increased significantly (both p-values<0.0001).

Conclusion. At 6 months, the majority of the patients had good VOs, including significant improvement in moderate VA, papilledema, and retinal venous dilatation. While nystagmus and esotropia increased significantly.

Keywords
hydrocephalus,
nystagmus,
papilledema,
posterior fossa tumours,
strabismus,
visual outcome

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INTRODUCTION

Brain tumors are the 19th most common malignancies, and the 12th leading cause of cancer-related mortality. [1] Among various brain tumors, those located in posterior fossa are more prevalent among children (54–70%) than adults (15–20%). [2] The posterior fossa

tumours (PFTs) are associated with grave consequences due to limited available space, and risk of brain stem nuclei involvement. [3]

PFTs often manifest with visual symptoms and signs that may adversely impact the visual afferent and efferent pathways. [4] The pressure of tumor on the visual pathway can result in reduced visual acuity (VA), loss of visual field, and impairment of eye movement. Additionally, increased intracranial pressure (ICP) may result from obstructive hydrocephalus, brain tumor mass effect, brain edema, and tumor infiltration into the leptomeninges. Raised ICP may result in papilledema and optic disc atrophy, leading to irreversible vision loss, even with hydrocephalus treatment. [4, 5]

Hydrocephalus can also result in abducens nerve paralysis, causing esotropia and horizontal diplopia. Trochlear nerve dysfunction can result in diplopia in the vertical or oblique direction, along with hypertropia. These tumors can interfere with the ability to maintain visual focus and affect the mechanisms responsible for vestibular and gaze stabilization, leading to skew deviation, nystagmus, and complex gaze palsies. [6]

Timely diagnosis of visual impairment is essential as vision loss caused by a brain tumor or its therapy is frequently permanent. [7] Gadgil et al. [4] and Peeler et al. [8] reported long-term (median 4-years and mean 20.5-months, respectively) visual outcomes (VOs) following surgical resection of PFTs in pediatric age group. Singh et al. described VOs in both pediatric and adult age groups; however, these were short-term outcomes (6-weeks). [6] Review of current literature suggested that further studies are required to evaluate the VOs, especially in both pediatric and adult age groups. Moreover, intermediate-term VOs have not been evaluated yet. Thus, the present study aimed to evaluate the VOs at 6-months following the index surgery in patients with PFTs.

Materials and methods

This retrospective study involved the review of electronic medical records of patients who had undergone surgical resection of PFTs, between August 2022 and January 2024, in the Department of Neurosurgery of a tertiary care hospital. The study included patients of all age groups, of either sex, and underwent surgical resection of PFTs with or without hydrocephalus. While, patients with recurrent PFTs, visual and ocular motor dysfunction unrelated to the tumor, those receiving chemo-radiotherapy as primary treatment, and incomplete examination data were excluded. The study was approved by the Institutional Ethics Committee, and consent of the patients was waived off due to retrospective nature of the study.

Participants and intervention

Over the period of 18-months, complete pre- and postoperative medical records were available in 50 patients fulfilling the eligibility criteria and thus, included in the study. The patients who presented with symptoms of hydrocephalus were subjected to magnetic resonance imaging (MRI) of brain to confirm the presence of posterior fossa mass as well as hydrocephalus, and subsequently underwent ventriculo-peritoneal (VP) shunt as emergency procedure. Based on the tumors, the patients underwent biopsy (< 25% of tumor volume [TV]), subtotal (25–90% of TV), near-total (>95% of TV), or gross total surgical resection, and the extent of resection was determined by postoperative MRI.

Following surgical resection, all patients with PFTs, except those with the World Health Organization grade 1 tumors, received concurrent chemo-radiotherapy. Chemotherapy included capsule temozolomide (75 mg/m2 of body size, once daily for Days 1-5, per oral) given for 6-weeks and later adjuvant for 6-months. Radiotherapy was given in a dose of 60 Gy over six weeks in 30–33 fractions (2 Gy/day for 5-days and then rest for 2-days).

Assessment

Preoperatively, the patients were assessed for color vision (on Ishihara test, present/absent), night vision (present/absent), VA (on Snellen chart), pupillary function (size, reactivity), papilledema grade, retinal findings (splinter hemorrhage [present/absent] and venous dilatation), strabismus (esotropia and hypertropia), and nystagmus (present/absent). Papilledema was graded from 0 to 5, by the modified Frisén Scale, with grade 0 and 5 suggesting normal optic disc and severe degree of edema, respectively. [9] Strabismus was described as any visible misalignment of the eyes associated with the tumor or treatment. The ellipsoid volume formula was used to calculate the TV (length × height × width × [π/6]). Postoperatively, at 6-months, all the above-mentioned parameters were assessed, and

improvement or deterioration in visual parameters were evaluated.

Statistical analyses

The data was analysed with SPSS (IBM, Armonk, NY, USA) version 23.0 for Windows. The categorical and continuous variables were represented as frequency (percentages) and mean (standard deviation), respectively. The association between categorical and continuous variables were assessed with Chi-square test and independent sample t-test, respectively. A two-tailed p-value <0.05 was regarded as statistically significant.

Results

The mean age of the study population was 31.64±19.97 years. The patients were mainly aged 1–10 years (22%) with slight female predominance (52%). The most common PFTs were brainstem glioma and pilocytic astrocytoma (each 18%). Of 50 patients, 40 (80%) had hydrocephalus and all of them underwent VP shunt procedure (Table 1).

Table 1. Demographic and disease characteristics.

Characteristics	n (=50)	%
Age, years		
1–10	11	22
11–20	8	16
21–30	7	14
31–40	6	12
41–50	8	16
51–60	6	12
>60	4	8
Sex		
Male	24	48
Female	26	52
Pathological diagnosis		
Brainstem glioma	9	18
Pilocytic astrocytoma	9	18
Medulloblastoma	7	14
Hemangioblastoma	6	12
CP angle vestibular schwannoma	5	10
Ependymoma	4	8
Posterior fossa metastasis	4	8
CP angle epidermoid cyst	3	6
CP angle meningioma	2	4
Anaplastic astrocytoma	1	2
Hydrocephalus	40	80
Shunt procedure	40	80

Preoperatively, color and night vision were present in 78% and 68% patients, respectively. Examination of VA revealed that patients mostly had moderate (38%) and normal vision (30%). The pupils were mainly 3 mm in size (84%) and reactive to light (74%). Grade 1 papilledema, splinter hemorrhage, and retinal venous dilatation were observed in 30%, 46%, and 76% patients, respectively. Moreover, nystagmus, esotropia, and hypertropia were present in 12%, 10%, and 10% patients, respectively. The mean TV was 40.48±10.26 mm3 (Table 2).

Table 2. Comparison of pre- and postoperative characteristics.

Characteristics	Preoperative (n=50)	Postoperative (n=50)	p-value
Color vision	39 (78%)	39 (78%)	1.000
Night vision	34 (68%)	29 (58%)	0.300
Visual acuity			
Normal Vision (6/6)	15 (30%)	23 (46%)	0.099
Good Vision (6/9 to 6/12)	9 (18%)	11 (22%)	0.617
Moderate Vision (6/18 to 6/60)	19 (38%)	8 (16%)	0.013
Poor Vision (<6/60)	7 (14%)	8 (16%)	0.779
Pupil size, mm			1.000
3	42 (84%)	42 (84%)	
4	8 (16%)	8 (16%)	
Pupil reactivity			
Normal	37 (74%)	39 (78%)	0.640
Non-reactive	8 (16%)	8 (16%)	1.000
Sluggish	5 (10%)	3 (6%)	0.461
Papilledema			
Grade 0	9 (18%)	27 (54%)	<0.0001
Grade 1	15 (30%)	4 (8%)	0.005
Grade 2	8 (16%)	7 (14%)	0.779
Grade 3	6 (12%)	4 (8%)	0.564
Grade 4	4 (8%)	0 (0%)	0.041
Grade 5	8 (16%)	8 (16%)	1.000
Splinter hemorrhage	23 (46%)	20 (40%)	0.545
Retinal venous dilatation	38 (76%)	22 (44%)	0.001
Nystagmus	6 (12%)	23 (46%)	<0.0001
Strabismus			
Esotropia	5 (10%)	23 (46%)	<0.0001
Hypertropia	5 (10%)	7 (14%)	0.538
Tumor volume, mm^3	40.48±10.26	8.35±1.89	<0.0001

Comparison of pre- and postoperative characteristics revealed no significant change in color and night vision (both p-values>0.05). Similarly, there was no significant change in pupil size and reactivity (both p-values>0.05). VA categorizes were comparable (all p-values>0.05), except significantly lesser proportion of patients with moderate vision observed postoperatively (p-value=0.013). Similarly, grades of papilledema did not change significantly postoperatively (all p-values>0.05), except significantly greater and lesser proportion of patients with grade 0 (p-value<0.0001) and grade 1 (p-value=0.005) as well as grade 4 papilledema (p-value=0.041), respectively. While, proportion of patients with splinter hemorrhage did not change significantly (p-value=0.545), significantly lesser proportion of patients had retinal venous dilatation postoperatively (p-value=0.001). Furthermore, postoperative incidence of nystagmus and esotropia increased significantly (both p-values<0.0001). Finally, the TV decreased significantly (p-value<0.0001) (Table 2). At 6-months, 16 (32%) patients had recurrence of PFTs.

Discussion

The principal findings of the present study suggested that PFTs were predominantly present in pediatric age group and included brainstem glioma as well as pilocytic astrocytoma. At 6-months, moderate VA, grades of papilledema, retinal venous dilatation, and TV improved significantly, while nystagmus and esotropia worsened significantly. Other outcome measures, including color vision, night vision, pupil size, pupillary reactivity to light, and splinter hemorrhage, were comparable with respect to preoperative status.

PFTs are reported in both adults and children with around two-third pediatric brain tumors originating from the posterior fossa. [10] In childhood, the predominant PFTs include pilocytic astrocytomas, ependymomas, and medulloblastoma, while tumors including lymphomas, metastatic lesions, and hemangioblastoma are more prevalent in adulthood. [11] Moreover, several PFTs occur in the cerebellopontine angle (CPA), consisting of arachnoid tissue, cerebrospinal fluid (CSF), facial and vestibulocochlear nerves, and the anterior inferior cerebellar artery. CPA tumors account for less than 10% and less than 1% of all intracranial tumors in adults and children, respectively. [12] Similarly, we observe comparable pattern of PFTs distribution in pediatric and adult age groups. Moreover, all the CPA tumors were diagnosed in adults. However, contrary to the literature, 70% PFTs were diagnosed in adults.

Complete surgical resection of the PFTs is the goal, to be followed by concurrent chemo-radiotherapy based on the histopathological findings. Over the last several years, better management of PFTs has reduced mortality, thereby increasing the number of long-term survivors. However, the survivors have visual deficit and decreased quality of life. [13] Thus, assessment of the VOs is critically important to allow for the best possible vision to survivors to better cope with the sequelae.

Mechanistically, the visual symptoms depend on the severity and duration of hydrocephalus and papilledema. [13] More than a quarter of the patients (80%) were diagnosed with hydrocephalus and an emergency VP shunt procedure was performed. Moreover, a quarter of the patients (24%) had grade 4 and 5 papilledema. Following the surgical excision of the tumor, none of the patients experienced hydrocephalus during the study period. At 6-months, grade 5 papilledema persisted, while none of patients had grade 4 papilledema. Thus, excision of the tumor mass and placement of VP shunt resulted in reduction of raised ICP and significantly decreased severity of papilledema, thereby improving the visual outcomes. Furthermore, persistence of the grade 5 papilledema highlights the irreversible nature of the neuronal injury.

At 6-months, there was an overall improvement in VA. The number of patients with normal and good vision increased from 30% to 46% and 18% to 22%, respectively, though this increase was not statistically significant. This increase in normal and good vision was associated with significant decrease in number of patients with moderate vision. However, the patients with preoperative poor vision persisted. Similar results were reported by other studies involving pediatric, [4, 8] as well as both pediatric and adult age groups. [6]

Various authors have reported VOs in benign PFTs, particularly low-grade gliomas. A study involving 51 patients with low-grade posterior fossa glioma reported that none of the patients had VA worse than 20/200, though 5.9% had visual field defect 15-years after initial diagnosis. [14] Another

study showed that none of the 34 survivors of low-grade glioma had VA worse than 20/200, although 5.9% had visual field defects at 10.7-years. [15] Peeler et al. demonstrated a low rate of visual impairment (4.7%) in patients with low-grade glioma at 20.5-months. [8] Similarly, we observed that only 2 of 20 patients with low-grade PFTs had poor vision <6/60, both pre- and postoperatively, thereby suggesting no deterioration in vision among patients with low-grade of PFTs.

PFT type is reported to be a significant determinant of VO. We found that patients with poor VA (n=8) had medulloblastoma (n=4), brainstem glioma (n=3), and posterior fossa metastasis (n=1). Similarly, patients with medulloblastoma and ependymoma have been demonstrated to have significantly worse VOs compared to those with juvenile pilocytic astrocytoma. [8] Medulloblastoma, brainstem glioma, and posterior fossa metastasis have aggressive growth patterns. Moreover, these tumors require more aggressive surgical resection as well as adjuvant chemo-radiotherapy. [16-18] More prolonged increases in ICP may put patients at greater risk of developing optic atrophy. Supporting these findings, all eight patients with poor VA had optic atrophy.

Additionally, visual impairment can be induced iatrogenically. The surgical resection of the tumor can result in impaired vision either through direct surgical damage to the optic pathway or due to perioperative visual loss resulting from a sudden decline in ICP or disruption of blood flow to the visual pathway. [19, 20] Radiation therapy may result in radiation-induced optic neuropathy and/or necrosis affecting the visual pathway. [21-23] Lastly, chemotherapy may lead to papilledema, optic neuritis, maculopathy, optic neuropathy, and cataracts. [24, 25]

A study reported that treatment of PFTs led to an increase in number of patients with nystagmus (from 5% to 23%), and strabismus (from 23% to 42.4%). [8] In another study, the authors observed that small esotropia mostly resolved spontaneously (80%), while 53% patients with moderate esotropia and 100% with large esotropia required surgical intervention. In these patients, the symptoms resolved, thereby suggesting an excellent prognosis for patients with post-operative esotropia. Hypertropia was observed in 14% patients, of which around half resolved spontaneously and remaining half required surgery resulting in correct eyes alignment in 40% patients, while 60% had continued symptomatic hypertropia with persistent diplopia despite multiple surgeries, thus suggesting a poorer prognosis for patients with post-operative hypertropia relative to those with esotropia. [4] Similarly, we observed that number of patients with nystagmus (from 12% to 46%), and esotropia (from 10% to 46%) increased significantly (both p-values<0.0001). Though patients with hypertropia increased as well (from 10% to 14%), it did not statistically significant level (p-value=0.538). However, we did not evaluate the outcome of strabismus surgery, as it was not performed in any of the patients during the study period. Increase in postoperative incidence of nystagmus and strabismus could be ascribed to more aggressive posterior fossa surgery and use of concurrent chemo-radiotherapy.

The present study had certain limitations. First, the study was retrospective in nature and control group could not BE used. Second, sample size was relatively small. Third, data related to visual fields was not available in all the patients, and thus not evaluated. Fourth, esotropia was not categorized into small, moderate, and large.

Conclusion

To conclude, surgical resection of PFTs followed by concurrent chemo-radiotherapy resulted in good VOs in majority of the patients, including significant improvement moderate VA, papilledema, retinal venous dilatation, and TV. While, color and night vision, pupil size and reactivity, hypertropia, and splinter hemorrhage did not change significantly. However, nystagmus and esotropia increased significantly. Adverse VOs were mainly related to hydrocephalus and papilledema, leading to optic atrophy.

Abbreviations

CPA	Cerebellopontine angle
CSF	Cerebrospinal fluid
ICP	Intracranial pressure
MRI	Magnetic resonance imaging
PFTs	Posterior fossa tumors
TV	Tumor volume
VA	Visual acuity
VOs	Visual outcomes
VP	Ventriculo-peritoneal

References

1. Ilic I, Ilic M (2023) International patterns and trends in the brain cancer incidence and mortality: An observational study based on the global burden of disease. Heliyon 9(7):e18222. https://doi.org/10.1016/j.heliyon.2023.e18222
2. Bose A, Prasad U, Kumar A, Kumari M, Suman SK, Sinha DK (2023) Characterizing Various Posterior Fossa Tumors in Children and Adults With Diffusion-Weighted Imaging and Spectroscopy. Cureus 15(5):e39144. https://doi.org/10.7759/cureus.39144
3. Kakar J, Ashraf J, Khan AA, Imran M, Rehmani MA, Ghori SA, et al (2020) The satisfactory surgical outcome of posterior fossa brain tumors in children at civil hospital, karachi. Asian J Neurosurg 15:377–81. https://doi.org/10.4103/ajns.AJNS_56_19.
4. Gadgil N, Edmond J, Stormes K, Lam S, Shah V (2019) Visual Complications of Pediatric Posterior Fossa Tumors: Analysis of Outcomes. Pediatr Neurol 92:48–54. https://doi.org/10.1016/j.pediatrneurol.2018.09.016.
5. Nuijts MA, Degeling MH, Stegeman I, Schouten-van Meeteren AYN, Imhof SM (2019) Visual impairment in children with a brain tumor: a prospective nationwide multicenter study using standard visual testing and optical coherence tomography (CCISS study). BMC Ophthalmol 19:220. https://doi.org/10.1186/s12886-019-1225-8.
6. Singh DK, Agrahari VK, Kaif M, Kumar R, Yadav K (2021) Visual outcome analysis in patients with posterior fossa tumours undergoing surgical treatment. Romanian Neurosurgery XXXV(2):174–9. https://doi.org/10.33962/roneuro-2021-027.
7. Moreno L, Bautista F, Ashley S, Duncan C, Zacharoulis S (2010) Does chemotherapy affect the visual outcome in children with optic pathway glioma? A systematic review of the evidence. Eur J Cancer 46(12):2253–9. https://doi.org/10.1016/j.ejca.2010.03.028.
8. Peeler CE, Edmond JC, Hollander J, Alexander JK, Zurakowski D, Ullrich NJ, et al (2017) Visual and ocular motor outcomes in children with posterior fossa tumors. J AAPOS 21(5):375–9. https://doi.org/10.1016/j.jaapos.2017.05.032.
9. Scott CJ, Kardon RH, Lee AG, Frisén L, Wall M (2010) Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. Arch Ophthalmol 128(6):705–11. https://doi.org/10.1001/archophthalmol.2010.94.
10. Loevner LA (1999) Imaging features of posterior fossa neoplasms in children and adults. Semin Roentgenol 34(2):84–101. https://doi.org/10.1016/s0037-198x(99)80024-8.
11. Santos de Oliveira R, Jucá CEB, Valera ET, Machado HR (2008) Hydrocephalus in posterior fossa tumors in children. Are there factors that determine a need for permanent cerebrospinal fluid diversion? Child´s Nervous System 24:1397–403. https://doi.org/10.1007/s00381-008-0649-x.
12. Bertot B, Steele WJ, Boghani Z, Britz G (2017) Diagnostic Dilemma: Cerebellopontine Angle Lipoma Versus Dermoid Cyst. Cureus 9(11):e1894. https://doi.org/10.7759/cureus.1894.
13. Peeler CE (2017) A Review of Visual and Oculomotor Outcomes in Children With Posterior Fossa Tumors. Semin Pediatr Neurol 24(2):100–03. https://doi.org/10.1016/j.spen.2017.04.007.
14. Armstrong GT, Conklin HM, Huang S, Srivastava D, Sanford R, Ellison DW, et al (2011) Survival and long-term health and cognitive outcomes after low-grade glioma. Neuro Oncol 13(2):223–34. https://doi.org/10.1093/neuonc/noq178.
15. Sonderkaer S, Schmiegelow M, Cartensen H, Nielsen LB, Muller J, Schmiegelow K (2003) Long-term neurological outcome of childhood brain tumors treated by surgery only. J Clin Oncol 21(7):1347–51. https://doi.org/10.1200/JCO.2003.08.009.
16. Iyer S, Ismail M, Tamrazi B, Salloum R, de Blank P, Margol A, et al (2022) Novel MRI deformation-heterogeneity radiomic features are associated with molecular subgroups and overall survival in pediatric medulloblastoma: Preliminary findings from a multi-institutional study. Front Oncol 12:915143. https://doi.org/10.3389/fonc.2022.915143.
17. Eisele SC, Reardon DA (2016) Adult brainstem gliomas. Cancer 122(18):2799–809. https://doi.org/10.1002/cncr.29920.
18. Sunderland GJ, Jenkinson MD, Zakaria R (2016) Surgical management of posterior fossa metastases. J Neurooncol 130(3):535–42. https://doi.org/10.1007/s11060-016-2254-2.
19. Peragallo JH (2018) Effects of brain tumors on vision in children. Int Ophthalmol Clin. 58(4):83–95. https://doi.org/10.1097/IIO.0000000000000237.
20. Ahn Y, Cho BK, Kim SK, Chung YN, Lee CS, Kim IH, et al (2006) Optic pathway glioma: outcome and prognostic factors in a surgical series. Childs Nerv Syst. 22(9):1136–42. https://doi.org/10.1007/s00381-006-0086-7.
21. Saha A, Salley CG, Saigal P, Rolnitzky L, Goldberg J, Scott S, et al. (2014) Late effects in survivors of childhood CNS tumors treated on head start I and II protocols. Pediatr Blood Cancer 61(9):1644–72. https://doi.org/10.1002/pbc.25064.
22. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J (2010) Radiation dose-volume effects of optic nerves and chiasm. Int J Radiat Oncol Biol Phys. 76(3):S28–35. https://doi.org/10.1016/j.ijrobp.2009.07.1753.
23. Donahue B (1992) Shot- and long-term complications of radiation therapy for pediatric brain tumors. Pediatr Neurosugery 18(4):207–17. https://doi.org/10.1159/000120664.
24. Al-Tweigeri T, Nabholtz JM, Mackey JR (1996) Ocular toxicity and cancer chemotherapy. Cancer 78(7):1359–73. https://doi.org/10.1002/(SICI)1097-

0142(19961001)78:7<1359::AID-CNCR1>3.0.CO;2-G.
25. Schmid KE, Kornek GV, Scheithauer W, Binder S (2006) Update on ocular complications of systemic cancer chemotherapy. Surv Ophthalmol 51(1):19–40. https://doi.org/10.1016/j.survophthal.2005.11.001.