Ophthalmological outcomes of patients treated for pineal region tumors

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OBJECTIVE The ophthalmological outcomes of children treated for pineal tumors have received limited attention in the literature.

METHODS This paper reviews the outcomes of 29 children treated for pineal and posterior third ventricular tumors in the contemporary era using chemotherapy, radiotherapy, and resection as defined by the histology and/or marker profile of the tumor.

RESULTS At the time of diagnosis, all patients except 1 had hydrocephalus and all had ophthalmological involvement. Papilledema was found in 69% of patients. Seventy-five percent of patients had partial or complete Parinaud's syndrome, and diplopia or blurred vision was noted in the remaining patients. Visual acuity was impaired in 8 patients. Outcomes were dependent on the histology of the tumor and the treatment required. Those patients who did not requiring resection showed a lower rate of ophthalmological worsening during treatment and greater long-term improvement, in particular with respect to up-gaze palsy. Patients who underwent resection for postchemotherapy residual disease or primary resection showed greater worsening during treatment and lesser degrees of recovery. All patients with impaired visual acuity improved with treatment.

CONCLUSIONS As the mortality of germ cell and other pineal tumors decreases, posttreatment morbidity remains, specifically that related to convergence nystagmus, accommodation, and diplopia. In addition to survival, ophthalmological morbidity should be reported in studies concerning the outcomes of treatment for pineal neoplasms.

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KEY WORDS pineal tumor; Parinaud's syndrome; accommodation; nystagmus; oncology

TUMORS in the pineal/posterior third ventricular region commonly present with visual disturbances caused by obstructive hydrocephalus and compression of the midbrain tectum. The cardinal ocular finding, supranuclear paresis of vertical gaze, was described in 1883 by the French ophthalmologist Henri Parinaud.⁸ Today, the term “Parinaud's syndrome” encompasses impaired up gaze, convergence-retraction nystagmus, lid retraction, and light-near dissociation.^{4,8}

With advancements in tumor-specific diagnosis using tumor biomarkers, microsurgical techniques, chemotherapy, and radiotherapy, the mortality associated with these tumors and their treatment has decreased. However, the visual disturbances and ocular mobility dysfunction ap-

parent prior to, and which remain after current treatment, have received limited attention in the neurosurgical literature.

The objective of this study was to describe the ophthalmological outcomes seen in children undergoing current treatment protocols for pineal/posterior third ventricular region tumors.

Methods

The prospectively maintained electronic databases of the Divisions of Pediatric Neurosurgery and Oncology at British Columbia's Children's Hospital were queried for patients younger than 18 years old who were treated for

ABBREVIATIONS NGGCT = nongerminomatous germ cell tumor.

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pineal region tumors between 1990 and 2014. We selected only patients who had tumors limited to the posterior third ventricle/pineal region who had had all of their treatments performed at British Columbia's Children's Hospital and had formal ophthalmological assessment(s) during and following their initial course of treatment. Patients with pineal cysts or tumors arising primarily from the mid-brain, its tectum, and the thalamus were excluded.

The reviewed patient data included patient age, sex, presentation, histological diagnosis, treatment course, complications, and outcomes. The assessed ophthalmological findings included the presence of complete or incomplete Parinaud's syndrome (up-gaze palsy, light-near dissociation, convergence-retraction nystagmus, and eyelid retraction), diplopia, visual field defects, visual acuity, strabismus, papilledema, and any ophthalmological interventions (glasses and ocular surgeries) performed to correct post-treatment visual impairment. We did not assess ophthalmological features at tumor recurrence/progression.

Approach to Management

Our approach to management was as follows: patients underwent treatment for hydrocephalus and tumor marker and cytology assessment.¹² For patients whose markers were diagnostic of nongerminomatous germ cell tumors (NGGCTs) and/or whose imaging was in keeping with germinoma,¹ chemotherapy was administered after hydrocephalus treatment. Following chemotherapy, if imaging showed residual tumor, patients were subjected to open biopsy and resection,¹¹ as per the open international studies at our institution (COG [Children's Oncology Group] ACNS0122; ACNS0232; ACNS1123). Those patients whose tumors were marker negative and whose imaging findings suggested a non-germ cell tumor diagnosis, or whose imaging findings were not characteristic of a pathological group, underwent open resection as per the protocols open at our institution as mentioned above. The extent of the resection was determined according to the tumor consistency and adherence to the tectum, habenula, pulvinar, and deep veins.

The University of British Columbia Research Ethics Board approved the study protocol. The results are presented as counts and percentages.

Results

Demographics and Clinical Presentation

The study cohort included 29 patients with a mean age of 12.6 years (range 5–17 years). Seventy-six percent of the patients were males. During the study period, an additional 18 patients were treated but did not meet the inclusion criteria.

The principal presenting symptoms included headache with nausea and/or vomiting in 27 patients (93%). One patient presented without these symptoms but complained of progressively decreasing vision, and 1 patient presented with progressive gait unsteadiness.

The majority of patients (97%) exhibited hydrocephalus on initial imaging. The 1 patient who did not present with hydrocephalus presented with a 6-month history of fatigue, weight loss, panhypopituitarism, and diplopia.

The average duration of symptoms prior to presentation was 8.4 weeks.

Initial imaging revealed intratumoral hemorrhage in 4 patients and multifocal disease on imaging in 2 patients, 1 of whom had metastases in the ventricular system and the other had intracranial and spinal metastases.

Diagnosis and Management

Hydrocephalus was managed by endoscopic third ventriculostomy in 19 patients, temporary external drainage in 5 patients, and ventriculoperitoneal shunt in 1 patient. Four patients underwent primary tumor resection.

The histological diagnoses were obtained from endoscopic biopsy (14 patients) or after open biopsy or resection (11 patients). Among the 4 patients who did not receive a tissue diagnosis, 3 patients were described as having NGGCTs and the fourth patient was treated as having a germinoma based on the tumor markers.^{2,9} The tumor pathologies are summarized in Table 1.

Definitive treatment depended on the pathological diagnosis.¹² Open resection was performed in 20 patients as a primary procedure, following chemotherapy, or prior to radiotherapy for residual masses persistent after chemotherapy. An occipital transtentorial approach was used in 75% of patients. Anterior and parietooccipital paramedian transcassal approaches were used in 4 patients based on the tumor extension into the mid and anterior third ventricle, and 1 patient underwent a supracerebellar infratentorial approach. Twenty percent of resections were total resections as determined by postresection MRI.

The only perioperative complication involved an equipment failure during 1 procedure, so the planned gross-total resection was abandoned and a subtotal resection was achieved. The patient did not suffer any adverse effects from this unexpected event. There were no perioperative deaths, and the 1-year postsurgery survival was 100%. The mean follow-up period was 5.6 years, with 22 years being the longest follow-up period.

Of the 20 surgical patients, 14 received chemotherapy prior to surgery and postresection radiation, 2 patients received chemotherapy prior to resection only, 2 patients received radiation following surgery, and 2 patients did not receive any adjuvant therapy.

Of the 9 patients who did not undergo resection, 7 patients received both chemotherapy and radiation and 2 patients were treated with chemotherapy alone. These patients' tumors showed a complete response to treatment.

TABLE 1. Histological and tumor marker diagnosis

Tumor Type	No. of Patients (%)
Germ cell tumor	22 (76)
Germinoma	9
Teratoma	3
Mixed teratoma & germinoma	6
Nongerminomatous malignant germ cell tumor	3
Yolk sac tumor	1
Pineoblastoma	6 (21)
Astrocytoma	1 (3)

Five patients died during follow-up. The mean time from presentation to death was 3.6 years (range 13 months to 6 years). All deaths were due to tumor recurrence following initial treatment.

Ophthalmological Features and Outcomes

The ophthalmological records were available for all patients after treatment completion, as well as during their treatment course (at presentation, following management of their hydrocephalus, during adjuvant therapy, and after resection). Ophthalmological findings at presentation were documented by neurologists, neurosurgeons, and/or oncologists using clinical testing methods for pupillary reaction, light-near reaction and accommodation, ocular mobility, and visual fields. Six patients were assessed by the ophthalmology service prior to any intervention.

At the time of presentation, 20 patients had papilledema. Of these, 10 patients had no evidence of Parinaud's syndrome. Eight patients had partial or complete Parinaud's syndrome without papilledema. Five patients had complaints of diplopia, and 3 patients had complaints of blurred vision. Visual acuity decreased in 8 of 13 patients in whom it was measured at presentation and ranged from 20/40 bilaterally to 20/100 in the right eye and 20/800 in the left in 1 patient.

The mean follow-up time to the last ophthalmological assessment was 3.3 years (range 18 months to 20 years) after presentation. No patient has shown recurrence at the time of this assessment. At this time, 22 patients (76%) showed residual ocular mobility disturbance; in 18 of these patients (62%), there was partial Parinaud's syndrome. Table 2 shows the frequency of each component of Parinaud's syndrome at 3 points in time: at presentation, during treatment, and at follow-up. The number of patients with diplopia, esotropia, and exotropia are also shown. Papilledema resolved in all affected patients following treatment.

Partial or complete Parinaud's syndrome was seen in 18 patients preoperatively, 25 patients during treatment, and 18 patients on completion of treatment (Table 2). Those patients who showed new features of Parinaud's syndrome during treatment included 3 patients who underwent resection (teratoma, postchemotherapy residual teratoma, and pineoblastoma). Two patients had a germinoma treated with chemotherapy only. The Parinaud's features of 5 patients improved at the completion of therapy. These included 3 patients with germinomas that were treated

medically, and 1 pineoblastoma and 1 teratoma after chemotherapy and resection.

Up-gaze paresis and light-near dissociation developed during treatment in up to one-third of patients and persisted at follow-up in 66% and 83% of patients, respectively. Convergence-retraction nystagmus was less common at presentation; however, when it was present or developed during treatment, it did not resolve. Eyelid retraction, the least common presenting feature, resolved in all patients at follow-up.

Diplopia was a common complaint on follow-up. Exotropia was not found at presentation, but developed during treatment in 8 patients. Seven of these patients underwent tumor resection in addition to adjuvant therapy. Six of these 8 patients had posttreatment strabismus surgery.

Esotropia was detected in 15 patients at the time of presentation and resolved following tumor treatment. Only 3 patients showed residual esotropia at the time of the last ophthalmological assessment.

A visual field defect was found in 1 of 23 patients. This patient exhibited enlarged blind spots and a right superior homonymous quadrantanopia following a left-sided inter-hemispheric occipital transtentorial approach for tumor resection following chemotherapy.

All patients with impaired visual acuity regained normal acuity by the time of the last assessment.

Following the completion of treatment, 7 patients required strabismus surgery to treat persistent diplopia. In 6 of these cases, diplopia was caused by exotropia, and 1 patient had right superior oblique palsy. Surgery to correct strabismus resulted in the complete resolution of diplopia in 3 patients, but 4 patients were left with residual diplopia that was not correctable with prisms. An additional 4 patients were treated with prisms only and had persistent diplopia that was, for the most part, well suppressed. Only 1 patient required continued patching for his symptoms.

Endoscopic third ventriculostomy and biopsy resulted in worsening visual blurring in 3 patients. Tonic down gaze occurred in 2 patients following endoscopic third ventriculostomy. All other patients tolerated this procedure without worsening.

The visual morbidities of the patients who underwent resection in addition to adjuvant therapy differed from those treated medically. Patients who required only chemotherapy and radiotherapy after diagnosis showed improvement in all of the features of Parinaud's syndrome

TABLE 2. Ophthalmological findings through the course of treatment*

Finding	At Presentation	Present During Treatment	Present at Follow-Up
Parinaud's syndrome	18	25	18
Upward-gaze palsy	16	14	10
Light-near dissociation	12	17	10
Convergence-retraction nystagmus	8	18	11
Eyelid retraction	3	1	0
Diplopia	18	19	11
Esotropia	15	9	2
Exotropia	0	6	8

* Data are presented as the number of patients.

FIG. 1. Comparison of the frequencies of the components of Parinaud's syndrome in patients whose definitive treatment included surgical resection (20 patients with NGGCT, teratoma, or pineal parenchymal tumor). Figure is available in color online only.

following treatment, especially up-gaze palsy. Light-near dissociation was the most frequent persisting feature. Patients who underwent resection had higher rates of persistent up-gaze palsy and convergence-retraction nystagmus at follow-up (Figs. 1 and 2). This group also showed the worsening of light-near dissociation as a result of their surgical intervention. Thirty-five percent of the patients who underwent resection developed persistent exotropia in comparison with 11% of nonsurgical patients. One patient had painful clonic convergence posttumor resection that eventually resolved. The patients who had clonic or tonic down gaze or convergence showed improvement after treatment with residual diplopia only.

At the last follow-up, 4 of 5 patients in whom a gross-total resection was achieved had 1 or more residual features of Parinaud's syndrome (up-gaze paresis, light-near dissociation, or convergence-retraction nystagmus). Nine of 15 patients in whom a less than gross-total resection was achieved exhibited persistent Parinaud's features.

Discussion

The neurosurgical literature provides limited details when describing the ophthalmological morbidity resulting from tumors of the pineal region in children.^{5,6} Contrary to previous suggestions that Parinaud's syndrome resolves

FIG. 2. Comparison of the frequencies of the components of Parinaud's syndrome in patients whose definitive treatment was chemotherapy and/or radiotherapy (9 patients with germinomas). Figure is available in color online only.

quickly following treatment, we found that persistent post-treatment visual morbidity is common.⁴ At the time of the last ophthalmological assessment, 76% of patients showed some lasting ocular mobility disturbance, with 62% having partial Parinaud's syndrome. Convergence-retraction nystagmus, when evident at the presentation or during treatment, was the most persistent feature. Diplopia was usually due to exophoria. When noted preoperatively, reduced visual acuity improved with the treatment of hydrocephalus and the tumor in all patients.

No treatment paradigm results in the complete resolution of preoperative visual morbidity, although those patients requiring only chemotherapy with or without radiotherapy are more likely to improve than those (also) undergoing tumor biopsy or resection. Tumor resection via the occipital transtentorial approach is associated with a higher rate of persistent postoperative convergence nystagmus, up-gaze palsy, and light-near dissociation. The rates are similar whether a gross-total resection is achievable or not.

Our findings are similar to those reported by Hart et al.⁴ In their surgical series of 20 patients (8 of whom were children) undergoing a subtentorial supracerebellar approach, visual disturbances were present in 35% of their study population preoperatively and 55% postoperatively. Persisting defects included up-gaze palsy and convergence-retraction nystagmus in 55%, esotropia/exotropia in 25%, disorder of vergence/accommodation in 20%, and visual field abnormalities (homonymous hemianopia) in 5% of patients.

Goldenberg-Cohen et al.³ reported a pediatric cohort of 6 children, all of whom had residual visual findings at follow-up (range 1.4–10 years after treatment). The ocular morbidity included limited upward gaze in all patients with light-near dissociation and convergence-retraction nystagmus in 5 patients.

Jia et al.⁶ reported their experience with applying the transcallosal interforneal approach to the pineal region. Parinaud's syndrome (the components were not specified) was present in 45 of 150 pediatric patients postoperatively, which resolved in 31 patients within 6 months. No further details were provided as to the extent of improvement or other visual impairments, specifically visual field defects, diplopia, and strabismus.

The incidence of enduring visual morbidity following resection of pineal/posterior third ventricular region is usually reported to be as low as 10%, with most visual morbidity being transient and resolving within a few days.^{5,7,10} These reports contrast our data and that of others. The reasons for this difference is not apparent as reports do not provide detailed ophthalmological outcomes. As suggested by Hart et al.,⁴ perhaps this is because the visual morbidity that is easiest to assess is up-gaze palsy and, as shown in our patients, this feature is the most likely to recover.

Based on our data and that of Hart et al.,⁴ the common surgical approaches (sub- or transtentorial) result in similar rates and types of postoperative morbidity. The series by Jia et al. does not provide sufficient detail to comment on the morbidity of the transcallosal interforneal approach.⁶

This report has several limitations. This is a retrospective review of patients with pineal region tumors who were fully managed and followed at British Columbia's Children's Hospital. We were not able to offer all patients a formal ophthalmological assessment prior to the initiation of treatment. As a result, this report may underestimate the frequency of the preoperative ophthalmological findings. Improving or worsening ophthalmological features during treatment, and the observation that patients commonly exhibited the features of Parinaud's syndrome and not the complete syndrome, complicate the description of morbidity. Compared with other series, a high proportion of patients received an operation as part of their treatment. This is a reflection of the proportion of true germinomas, NGGCTs, mixed germ cell tumors, and non-germ cell tumors in this series.

Conclusions

Tumors of the pineal region and posterior third ventricle commonly present with ophthalmological findings and papilledema due to obstructive hydrocephalus. With the current diagnostic and treatment techniques, the mortality of these tumors has fallen, leaving ocular morbidity among those outcomes that impact a patient's day-to-day function. We suggest that future studies on the outcomes of pineal tumor management report outcomes, including ophthalmological outcomes in addition to neuropsychological performance, quality-of-life measures, and survivorship, among others.

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Disclosures

The authors report no conflict of interest concerning the materi-

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Author Contributions

Conception and design: Cochrane, Lyons. Acquisition of data: Hankinson, Hukin. Analysis and interpretation of data: Cochrane. Drafting the article: Hankinson. Critically revising the article: all authors. Reviewed submitted version of manuscript: Lyons. Approved the final version of the manuscript on behalf of all authors: Cochrane. Statistical analysis: Hankinson.

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