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
pineal region tumors between 1990 and 2014. We selected only patients who had tumors limited to the posterior third ventricle/pineal region who 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 midbrain, 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 posttreatment 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.29 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 transcallosal 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>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germ cell tumor</td>
<td>22 (76)</td>
</tr>
<tr>
<td>Germinoma</td>
<td>9</td>
</tr>
<tr>
<td>Teratoma</td>
<td>3</td>
</tr>
<tr>
<td>Mixed teratoma &amp; germinoma</td>
<td>6</td>
</tr>
<tr>
<td>Nongerminomatous malignant germ cell tumor</td>
<td>3</td>
</tr>
<tr>
<td>Yolk sac tumor</td>
<td>1</td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

TABLE 1. Histological and tumor marker diagnosis
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 interhemispheric 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**

<table>
<thead>
<tr>
<th>Finding</th>
<th>At Presentation</th>
<th>Present During Treatment</th>
<th>Present at Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parinaud’s syndrome</td>
<td>18</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Upward-gaze palsy</td>
<td>16</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Light-near dissociation</td>
<td>12</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Convergence-retraction nystagmus</td>
<td>8</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Eyelid retraction</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diplopia</td>
<td>18</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Esotropia</td>
<td>15</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Exotropia</td>
<td>0</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

* Data are presented as the number of patients.
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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.\textsuperscript{5,6} Contrary to previous suggestions that Parinaud’s syndrome resolves

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.

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. At the time of the 
last ophthalmological assessment, 76% of patients showed 
some lasting ocular mobility disturbance, with 62% hav- 
ing 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, re-
duced visual acuity improved with the treatment of hydro-
cephalus and the tumor in all patients.

No treatment paradigm results in the complete res-
olution of preoperative visual morbidity, although those 
patients requiring only chemotherapy with or without ra-
diotherapy 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 nys-
tagmus, up-gaze palsy, and light-near dissociation. The 
 rates are similar whether a gross-total resection is achiev-
able or not.

Our findings are similar to those reported by Hart et 
al. In their surgical series of 20 patients (8 of whom were 
children) undergoing a subtentorial supracerebellar ap-
proach, visual disturbances were present in 35% of their 
study population preoperatively and 55% postoperatively. 
Persisting defects included up-gaze palsy and conver-
gence-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. 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 ocu-
lar morbidity included limited upward gaze in all patients 
with light-near dissociation and convergence-retraction 
nystagmus in 5 patients.

Jia et al. reported their experience with applying the 
transcallosal interforniceal 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 follow-
ing resection of pineal/posterior third ventricular region 
is usually reported to be as low as 10%, with most visu-
all morbidity being transient and resolving within a few 
days. These reports contrast our data and that of oth-
ers. The reasons for this difference is not apparent as re-
ports do not provide detailed ophthalmological outcomes. 
As suggested by Hart et al., 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 like-
ly to recover.

Based on our data and that of Hart et al., the common 
surgical approaches (sub- or transtentorial) result in simi-
lar 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 interforniceal ap-
proach.

This report has several limitations. This is a retrospec-
tive review of patients with pineal region tumors who were 
fully managed and followed at British Columbia’s Child-
ren’s Hospital. We were not able to offer all patients a 
formal ophthalmological assessment prior to the initia-
tion of treatment. As a result, this report may underestimate 
the frequency of the preoperative ophthalmological find-
ings. Improving or worsening ophthalmological features 
during treatment, and the observation that patients com-
monly exhibited the features of Parinaud’s syndrome and 
not the complete syndrome, complicate the description of 
morbidity. Compared with other series, a high propor-
tion 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 tu-
mors in this series.

Conclusions

Tumors of the pineal region and posterior third ven-
tricle commonly present with ophthalmological findings 
and papilledema due to obstructive hydrocephalus. With 
the current diagnostic and treatment techniques, the mor-
tality 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 neuropsycho-
logical performance, quality-of-life measures, and survi-
vorship, among others.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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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