Neuroendoscopic findings in patients with intracranial germinomas correlating with diabetes insipidus

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Object. Intracranial germinomas commonly occur in the pineal region, the floor of the third ventricle (hypothalamus), or both, and they are often associated with diabetes insipidus (DI). The authors conducted a study to correlate preoperative DI with the endoscopic and magnetic resonance (MR) imaging evidence of tumor on the third ventricle floor.

Methods. The authors reviewed hospital records, office charts, and MR imaging studies obtained in patients in whom a biopsy sampling procedure was performed with or without endoscopic third ventriculostomy (ETV) at Children’s Hospital, Birmingham, Alabama between May 1998 and July 2002. Ten patients with the pathological diagnosis of pure germinoma were identified. Preoperative MR imaging findings and presenting symptoms were correlated with intraoperative neuroendoscopic findings.

Seven patients presented with symptomatic hydrocephalus and underwent concomitant ETV. Six patients presented with DI and MR imaging evidence of involvement of the third ventricle floor. Two patients presented with DI and no initial MR imaging evidence of neoplastic involvement of the third ventricle floor; in both there was endoscopic evidence of neoplastic involvement of the floor of the third ventricle. In two children without DI, neither MR imaging nor endoscopic evidence of involvement of the third ventricle floor was observed.

Conclusions. In the authors’ experience with intracranial germinoma, endoscopic tumor biopsy sampling, and ETV provide an effective, safe, and minimally invasive means of obtaining diagnostic tissue and treating any concomitant hydrocephalus. The authors found that preoperative DI is an absolute predictor of neoplastic involvement of the hypothalamus regardless of MR imaging findings. Therefore, in the setting of DI and intracranial germinoma without neuroimaging evidence of hypothalamic involvement, germinomatous involvement of the hypothalamus should be assumed present, if not confirmed endoscopically at the time of biopsy sampling or third ventriculostomy, when devising adjuvant treatment plans for such patients.

KEY WORDS: brain tumor, diabetes insipidus, endoscopy, germinoma, hydrocephalus, pediatric neurosurgery

CENTRAL nervous system germinomas most commonly occur in the pineal region, third ventricle, or suprasellar region but may in rare cases appear in the basal ganglia, thalamus, brainstem, cerebellopontine angle, cranial nerves, cerebral hemispheres, or in the spinal cord. Patients with pineal region tumors typically present with signs and symptoms of hydrocephalus (headache, vomiting, or diplopia) due to obstruction of the cerebral aqueduct. In patients with DI and a pineal mass, suprasellar or anterior third ventricular involvement may be detected on MR imaging. Indeed, it may be argued that the simultaneous presence of a pineal and anterior third ventricle floor/suprasellar lesion is pathognomonic for intracranial germinoma. In this series of 10 patients with CNS germinomas of the pineal and/or hypothalamic region, we carefully evaluated the third ventricle floor for evidence of disease at the time of endoscopic biopsy sampling. We correlated our endoscopic findings with MR imaging features and with the clinical presence of DI to identify the best means for determining disease extent in this selected group of patients.

Clinical Material and Methods

Patient Population

We reviewed office charts, hospital records, and neuroimaging studies of patients in whom a third ventricle region or pineal tumor biopsy sample was obtained with
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or without ETV between May 1998 and July 2002 at Children’s Hospital, Birmingham, Alabama. In this 51-month period, a pathological diagnosis of pure germinoma of the pineal region and/or third ventricle was demonstrated in 10 patients (three female, seven male; median age 13 years). During this period, using similar endoscopic techniques, non-germinomatous germ cell tumors of the third ventricle region were diagnosed in three patients, who are not included in this report. Initial Gd-enhanced MR imaging findings and presenting symptoms were correlated with endoscopic findings. Successful treatment of the hydrocephalus was indicated by the following: absence of symptoms of raised intracranial pressure and significant reduction or normalization of ventricle size.

Surgical Technique

The exact method of endoscopic tumor biopsy sampling and ETV varied but ultimately evolved to the following technique. After the induction of general anesthesia, the patient is kept supine. Following adequate sterile skin preparation, a 4-cm vertical skin incision is made anterior to the coronal suture 2 cm lateral to the midline. In patients requiring ETV and biopsy sampling of a pineal region tumor, two burr holes are placed, one each at the anterior and posterior aspects of the incision. Via the anterior burr hole, the dura mater is opened sharply, and the pia is coagulated and disrupted. A No. 12.5 French introducer sheath is passed into the ipsilateral frontal horn of the lateral ventricle; it is left in place, and the same procedure is performed via the other burr hole. Because the biopsy procedure can cause bleeding that obscures visualization, the ETV is performed first. A rigid 0° ventriculoscope is then guided down the posterior tract, and pertinent landmarks in the lateral and third ventricles are identified. Between the mammillary bodies and infundibular recess, a midline perforation is made using endoscopic scissors. The endoscopic spreader is then used to dilate the fenestration in the floor as well as the membrane of Liliequist. This reveals the basilar artery complex, brainstem, and preponine cistern. The scope is removed and the tract is inspected on the way out for parenchymal bleeding. The endoscope is then inserted via the anterior burr hole, which allows for better access to the posterior third ventricle and pineal region. Under direct visualization, the biopsy sample is obtained using cup forceps. Routinely, multiple biopsy specimens are taken from various regions of the mass. The scope is removed, and, once again, the tract is inspected while exiting for parenchymal bleeding. Gelfoam is placed in both burr holes, and the skin is closed in two layers. External ventricular drains are not routinely placed.

Results

Seven patients presented with hydrocephalus and underwent concomitant biopsy sampling and ETV. All procedures were performed at our institution. Demographic data are summarized in Table 1. The majority of patients presented with symptoms of hydrocephalus (headache and vomiting) or hypothalamic involvement (uncompensated DI with hyponatremia or early compensated DI with increased urine output and an increased thirst mechanism). Six patients presented with DI and third ventricle floor involvement identified on MR imaging. Intraoperative endoscopic findings confirmed this. Two patients (Cases 5 and 8) presented with pineal lesions, DI, and no MR imaging–documented involvement of the third ventricle floor; however, disease on the floor of the third ventricle was clearly visible during endoscopic biopsy sampling of the pineal lesion. Because of this finding, disseminated disease was suspected and the cases were relegated to a more aggressive treatment arm that included craniospinal irradiation. Two children presented with a pineal mass without DI, and MR imaging revealed no involvement of the third ventricle floor. This was confirmed by direct endoscopic observation during the biopsy procedure. Spinal dissemination at presentation was absent in all patients, as documented on MR imaging. The mean follow-up period was 24 months. All patients presenting with DI (regardless of severity of symptoms) experienced transient exaggeration of its symptoms postoperatively. In four patients urine output was increased with an elevated sodium level within 24 hours, two within the week, and two within the month. All but one continue to receive regular doses of desmopressin. In all seven patients who underwent ETV symptoms of raised intracranial pressure resolved and there was no evidence of hydrocephalus on follow-up MR images. One patient who presented with severe encephalopathy and DI died of chemotherapy-related toxicity. Six of the remaining eight patients have completed treatment and three are still undergoing therapy. All undergo follow up in both the pediatric neurosurgery and neurooncology clinics. The tumors have responded to treatment in all cases, and there has been no evidence of postoperative intraventricular or subarachnoid dissemination.

Illustrative Case

Case 8

At the time of his initial visit, this 14-year-old African-American boy presented with headache, diplopia, polydipsia, and polyuria. Neurological examination demonstrated left-sided sixth cranial nerve palsy, and the initial sodium level was 144. Magnetic resonance imaging revealed an enhancing pineal lesion causing obstructive hydrocephalus. No other lesions were observed (Fig. 1). The following day, the child underwent uneventful ETV, and a biopsy sample of the pineal region tumor was obtained. During this procedure, tumor deposits were seen in the infundibular recess, and biopsy specimens were taken as well. After recovering from surgery, the patient underwent a full staging evaluation that included spinal MR imaging, lumbar puncture for routine studies, CSF cytology, tumor markers, and serum tumor markers. A classification of low-risk disseminated disease was established, and the patient underwent four cycles of chemotherapy; after this, craniospinal irradiation was performed with boost doses to the tumor field (off study but according to the POG Study 9530 for malignant CNS germ cell tumors). As with the other patients, the child required desmopressin therapy for control of DI; however, he has recently been weaned from this without evidence of polydipsia or polyuria, and the sodium balance remains normal. Follow-up MR imaging revealed
## TABLE 1
Summary of demographic and pre-, intra-, and postoperative data obtained in 10 patients with CNS germinomas*

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age, (yrs), Sex</th>
<th>Preop Findings</th>
<th>Op Data</th>
<th>Postop Findings</th>
<th>FU (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptoms</td>
<td>MR Imaging</td>
<td>Type</td>
<td>Findings</td>
<td>Symptoms</td>
</tr>
<tr>
<td>1</td>
<td>21, M HA, N/V, Parinaud syndrome</td>
<td>1) pineal lesion, 2) 3rd vent floor clear, 3) HCP</td>
<td>biopsy &amp; ETV</td>
<td>clean 3rd vent floor</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>11, M DI</td>
<td>1) pineal lesion, 2) suprasellar lesion, 3) no HCP</td>
<td>biopsy</td>
<td>tumor bulging through foramen of Monro</td>
<td>DI</td>
</tr>
<tr>
<td>3</td>
<td>12, F HA, N/V, DI</td>
<td>1) pineal lesion, 2) enhancing 3rd vent floor, 3) HCP</td>
<td>biopsy &amp; ETV</td>
<td>tumor studding on 3rd vent floor</td>
<td>DI</td>
</tr>
<tr>
<td>4</td>
<td>5, M precocious puberty, DI</td>
<td>1) no pineal lesion, 2) mass on 3rd vent floor, 3) no HCP</td>
<td>biopsy</td>
<td>mass on 3rd vent floor</td>
<td>weight gain, hypothyroidism</td>
</tr>
<tr>
<td>5</td>
<td>12, F N/V, hemiparesis, DI</td>
<td>1) pineal lesion, 2) BG lesion, 3) HCP</td>
<td>biopsy &amp; ETV</td>
<td>tumor studding on 3rd vent floor</td>
<td>hemiparesis better, DI</td>
</tr>
<tr>
<td>6</td>
<td>21, M HA, ataxia, LOC, DI</td>
<td>1) pineal lesion, 2) enhancing 3rd vent floor, suprasellar region, 3) HCP</td>
<td>biopsy &amp; ETV</td>
<td>tumor studding on 3rd vent floor</td>
<td>DI</td>
</tr>
<tr>
<td>7</td>
<td>10, F encephalopathy, hemiparesis, DI diplopia, HA, DI</td>
<td>1) no pineal lesion, 2) BG lesion, 3) mass on 3rd vent floor, 4) no HCP</td>
<td>biopsy</td>
<td>mass on 3rd vent floor</td>
<td>DI</td>
</tr>
<tr>
<td>8</td>
<td>14, M</td>
<td>1) pineal lesion, 2) 3rd vent floor clear, 3) HCP</td>
<td>biopsy &amp; ETV</td>
<td>tumor studding on 3rd vent floor</td>
<td>DI</td>
</tr>
<tr>
<td>9</td>
<td>14, M HA, N/V, DI</td>
<td>1) pineal lesion, 2) mass on 3rd vent floor, 3) HCP</td>
<td>biopsy &amp; ETV</td>
<td>tumor studding on 3rd vent floor</td>
<td>DI</td>
</tr>
<tr>
<td>10</td>
<td>16, M HA, N/V, diplopia</td>
<td>1) pineal lesion, 2) 3rd vent floor clear, 3) HCP</td>
<td>biopsy &amp; ETV</td>
<td>clean 3rd vent floor</td>
<td>none</td>
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</tbody>
</table>

* BG = basal ganglia; FU = follow up; HA = headache; HCP = hydrocephalus; LOC = loss of consciousness; N/V = nausea and vomiting; 3rd vent = third ventricle.
no evidence of hydrocephalus or enhancing lesions within the CNS.

**Discussion**

Numerous retrospective case series of pineal tumors with or without third ventricular floor lesions have been extensively reported in the neurosurgical, endocrine, medical oncology, and radiation oncology literature. Less common, but more recently reported, has been the neuroendoscopic management of these lesions. Endoscopic biopsy sampling of ventricle lesions was initially described in 1978 by Fukushima, using his “ventriculofiberscope,” who reported the successful biopsy sampling of third and lateral ventricle tumors. More recently, Pople, et al., demonstrated success when performing simultaneous endoscopic biopsy sampling and ETV in 34 patients with pineal tumors (six germinomas). Pathological diagnosis was established in 94% of the patients in the entire series. Souweidane, et al., also reported the successful procurement of biopsy specimens in 12 patients with third ventricle lesions, as has Gangemi, et al., in five patients (zero and two germinomas, respectively).

Intracranial germ cell tumors comprise less than 5% of all reported brain tumors and tend to occur in individuals between the ages of 10 and 21 years. The vast majority develop in the midline, specifically the third ventricle and pineal region, and may also spread to or involve any region of the CNS. For treatment, these tumors are classified into two groups: germinomas and nongerminous germ cell tumors. This latter group consists of embryonal cell carcinomas, endodermal sinus tumors, mature and immature teratomas, choriocarcinomas, and mixed germ cell tumors. Approximately 40% of all germ cell tumors are germinomas.

Germinomas are known to present occasionally with simultaneous involvement of the pineal region and the suprasellar area. Authors of previous reports have estimated that as many as 10% of germinomas present in this manner. Presenting symptoms tend to be related to the location and not the cell type. Because of the pineal region–induced obstruction of the cerebral aqueduct, hydrocephalus occurs, and patients may present with headache, vomiting, diplopia, Parinaud syndrome, and papilledema. Patients with germinomas involving the suprasellar area or anterior third ventricle may also present with symptoms of hypothalamic–pituitary axis dysfunction such as DI, delayed growth, menstrual irregularities, or precocious puberty as well as signs of visual apparatus compression such as disturbance of visual acuity or of the visual fields. Assessment of CSF protein markers may assist in the pathological classification of the tumor as well. Although germinomas tend to be negative for AFP, placental alkaline phosphatase may be detected in CSF, and β-HCG may be detected as well.

With little exception, DI occurs when these lesions involve the hypothalamic–pituitary axis. It is well known by our endocrine colleagues that patients with idiopathic DI must undergo close follow-up imaging because occult intracranial germinomas may occur later. Indeed, the findings in our Case 2 fall into this category. Otherwise, all other patients presented with DI, hydrocephalus, or both. In their 2001 paper on endoscopic biopsy sampling of pineal lesions of varying histology, Pople, et al., reported on one patient with hydrocephalus, DI, and MR imaging evidence of both a pineal and suprasellar lesion. Of note, they did mention obtaining biopsy specimens of tumor on the floor of the third ventricle as well as the pineal region in this patient. In an extensive review of the literature, this was the only mention of a third ventricle floor tumor viewed neuroendoscopically in this setting. In their series of 30 patients, Gaab and Schroeder reported a pathological diagnosis of germinoma in one patient in whom there was evidence of DI and MR imaging documentation of a pineal and suprasellar lesion; again, however, there was no mention of viewing the floor of the third ventricle through the endoscope. In reviewing 253
cases of primary CNS germinomas, Jennings, et al., concluded that any sign of hypothalamicpituitary axis involvement warrants craniospinal irradiation, regardless of appearance on MR imaging. Whole-neuraxis irradiation is not a benign therapy, and the issue of prophylactic radiotherapy in this setting is controversial.15,30,39,47,50,55

Germinomas have proven to be uniquely radio- and chemosensitive and it is well known that tumor resection is unnecessary. In the setting of obtrusive hydrocephalus, ETV can be performed along with a biopsy procedure. In our cases in which evidence of hydrocephalus was absent, ETV was not performed; however, it was performed through tumor along the floor of the third ventricle in patients with tumor burden in that region and who required CSF diversion. A small area on the floor of the third ventricle could be cleared away to allow ETV. None of the seven patients who underwent concomitant ETV during endoscopic biopsy sampling required a secondary procedure.

Standard treatment of intracranial germinomas consists of radio- and chemotherapy. Whole-brain irradiation alone is associated with long-term survival rates as high as 90%.15,33 Success has been reported in studies involving smaller doses of radiation to the brain, spine, and tumor site in combination with chemotherapy.15 Local treatment only is used if no evidence of dissemination exists. All of our patients were treated according to the recent POG Study 9530. In the pure germinoma arm, patients were stratified to one of two groups: those with disseminated or nondisseminated disease. After four cycles of chemotherapy that included administration of cisplatin, etoposide, vincristine, and cyclophosphamide every 3 weeks, patients either underwent involved-field radiotherapy (nondisseminated disease group) or craniospinal irradiation with a boost to the involved field (disseminated disease group). Cytological examination of the CSF was negative in all patients. Both serum and CSF tumor markers and in all cases β-HCG was equal to or higher than serum β-HCG. Cerebrospinal fluid β-HCG was greater than 50 mIU/ml in two patients who were then considered at a high risk and underwent a more aggressive chemotherapy regimen according to the POG 9530 protocol. In these patients elevated CSF β-HCG was present but AFP was negative and histological features were consistent with pure germinoma. Controversy surrounds whether these patients should be considered to harbor mixed germ cell tumors because there is no absolute definition of the exact level of β-HCG considered too high for germinoma. In these patients the value was less than 100 mIU/ml, and there were no other indications for mixed germ cell tumor; therefore, we considered the lesions to be germinoma. Craniospinal irradiation was administered to eight patients with evidence of dissemination or multicentric disease. Dissemination was defined as a pineal mass and either endoscopic or MR imaging evidence of tumor involving the floor of the third ventricle (Table 2). Multicentric disease was defined as third ventricle region mass and parenchymal involvement (basal ganglia).

It is worth noting that the presence of preoperative DI is a positive predictor for postoperative long-term vasopressin requirement.38 In our series, all but one patient presented with DI. In this patient there was no sign of DI postoperatively in contrast to the remaining eight. It is crucial to follow closely the urine output postoperatively, both in the immediate period and for as long as a month after surgery. Serum sodium, although compensated preoperatively, was noted to increase to abnormal levels if left untreated in the postoperative period for up to 1 month.

The lesions identified on MR imaging involving the suprasellar region (Cases 2 and 6) were thought to be the cause of DI due to involvement of the hypothalamopituitary axis. These patients were treated off-study, according to the POG Study 9530 protocol for disseminated germinoma that included craniospinal irradiation. Authors of germinoma and pineal tumor series have detailed successful treatment involving local only or limited radiation delivery to the ventricular system in patients with germinomas presenting with DI.47,55 We propose that the patients in the previous studies may have had similar endoscopic findings had this procedure been conducted and yet out-

<table>
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<tr>
<th>Case No.</th>
<th>Evidence of 3rd Vent Floor Involvement</th>
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<th>Cytology Result</th>
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<th>Postop Therapy</th>
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</table>

* Chemo = chemotherapy; radio = radiotherapy.
† The high/low risk cutoff at Children’s Hospital of Alabama is 50 mIU/ml.
‡ A negative result indicates the absence of germinoma cells found in the CSF.
§ Two patients in whom β-HCG was greater than 50 mIU/ml were treated with a more aggressive chemotherapy regimen according to the POG 9530 protocol.
∥ Craniospinal irradiation was performed in patients with evidence of dissemination or multicentric disease.
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come was similar to that in later series in which patients underwent craniospinal irradiation. Therefore, stratification into the disseminated disease treatment arm and provision of craniospinal irradiation may be overly aggressive as well as unnecessary when endoscopic evidence alone indicates the presence of third ventricle disease and a pineal region tumor. More limited treatment involving either the anterior third ventricle/suprasellar region or entire ventricular system may be more appropriate and spare the patients the well-known potential complications of craniospinal irradiation.

Conclusions

We have found that the vast majority of our patients with pineal region or third ventricle germinomas present with either florid or compensated DI. The presence of DI predicts tumor involvement of the floor of the third ventricle independent of MR imaging findings. In our experience, endoscopic evaluation of the third ventricle floor revealed disease not demonstrated on MR images in patients with DI. In the setting of obstructive hydrocephalus and neoplastic involvement of the third ventricle floor, ETV can be performed safely and effectively once adequate tumor has been removed from the floor. Although it seems clear based on our experience, not to mention being simply intuitive, that DI predicts hypothalamic involvement, it is unclear whether a subset of patients with germinoma exists in which DI develops without hypothalamic involvement. Whether DI or endoscopic inspection is the more sensitive means of detecting hypothalamic/third ventricle floor involvement is unknown. If the presence of tumor deposits on the floor of third ventricle in the setting of pineal region germinoma should influence stratification into various adjuvant therapy protocols, then knowing which means is the most sensitive for detecting hypothalamic/third ventricle floor involvement likely would be of some importance.

References


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