Infratentorial complications following preresection CSF diversion in children with posterior fossa tumors

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Object
This report presents the incidence, causes, and morbidity and mortality of infratentorial complications following CSF diversion before resection in children with posterior fossa tumors.

Methods
The medical records of 437 children admitted to Abo El-Reesh Pediatric University Hospital with a diagnosis of posterior fossa tumor between 2005 and 2012 were retrospectively reviewed. Seven children developed neurological deterioration following CSF diversion due to infratentorial complications. Computed tomography scans revealed intratumoral hemorrhage (ITH) in 5 cases, while upward transtentorial herniation (UTH), as evidenced by obliteration of the quadrigeminal and ambient cisterns, was diagnosed in 2 cases.

Results
Hydrocephalus was noted in 381 patients, and 301 patients underwent CSF diversion before resection. A ventriculoperitoneal (VP) shunt was used in 214 patients, and 6 children (2.8% of shunted cases) deteriorated neurologically (4 due to ITH and 2 due to UTH). Endoscopic third ventriculostomy (ETV) was performed in 87 patients, 1 of whom developed ITH (1.1% of the patients undergoing ETV). Six patients deteriorated within 8 hours (85.7%), whereas 1 patient, the only survivor, deteriorated after 24 hours. The incidence of infratentorial complications between VP shunts and ETVs was not found to be significantly different (p = 0.659). There was a higher risk of such complications in large posterior fossa tumors (diameter ≥ 4 cm) extending close to the tentorial incisura, especially in patients with severe hydrocephalus and significant peritumoral edema.

Conclusions
Infratentorial complications (ITH and UTH) in children with posterior fossa tumors are not uncommon (2.3%) after preresection CSF diversion (VP shunt or ETV) and are associated with a very poor prognosis in most cases, even with surgical intervention.

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Key Words
intratumoral hemorrhage; posterior fossa tumor; CSF diversion; upward transtentorial herniation; hydrocephalus

Children with posterior fossa tumors frequently present with severe headache and vomiting, which are usually the result of obstructive hydrocephalus.\(^{11,16}\) At the time of diagnosis, hydrocephalus is present in approximately 70% to 80% of patients with fourth ventricle tumors.\(^{4,5,11,32}\) In 1 study conducted in India, hydrocephalus was noted in all cases with posterior fossa tumors.\(^{16}\)

Although there are many studies on the management of hydrocephalus in children with posterior fossa tumors, there is no consensus regarding optimal hydrocephalus management.\(^{7,10,23,25,28,29,31}\) There are two opposing strategies for addressing preoperative hydrocephalus in children with posterior fossa tumors. Traditionally, routine preoperative CSF diversion has been advocated, followed by tumor resection. Ventricular shunts were first introduced in the early 1960s.\(^{1,13}\) Later, external ventricular drainage (EVD),\(^{9,28,39}\) subcutaneous ventricular catheter reservoir,\(^{38}\) and more recently, endoscopic third ventriculostomy (ETV) were alternatively recommended to avoid many shunt-associated complications.\(^{5,36}\) On the other hand, recent recommendations support directly addressing the obstructing posterior fossa tumor with primary resection at the earliest opportunity.\(^{16,26,40}\)

Preregression ventriculoperitoneal (VP) shunt placement, or less often ETV, followed by tumor excision after 1 or 2 weeks is the most common approach used in our

Abbreviations
ETV = endoscopic third ventriculostomy; EVD = external ventricular drainage; ICP = intracranial pressure; ITH = intratumoral hemorrhage; UTH = upward transtentorial herniation; VP = ventriculoperitoneal.


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pediatric university hospital. The potential advantages of this strategy include the following. Preoperatively, after relieving the manifestations of acute hydrocephalus, there is remarkable improvement in the general condition of the child, which allows definitive tumor resection to be performed in a planned, elective manner that is more convenient for our overburdened hospital with a long operative waiting list due to limited resources. Moreover, postoperative elevations of intracranial pressure (ICP) are reduced with a lower incidence of pseudomeningocele formation and CSF leakage, and hence a shortened hospital stay.

However, a number of complications have been associated with CSF diversion, including: supratentorial intracranial hematomas (e.g., extradural, subdural, intracerebral, and intraventricular hemorrhage); many shunt-associated complications, such as malfunction, infection, multiple abdominal complications, long-term shunt dependence, and metastases into the peritoneal cavity or vascular system; and infratentorial complications, e.g., intratumoral hemorrhage (ITH) and upward transtentorial herniation (UTH). Several case reports have been published describing the serious and mostly fatal infratentorial complications (ITH and/or UTH) that may occur as a result of preresectional CSF diversion, either by ventricular shunting or ETV in patients with posterior fossa tumors. Therefore, the actual incidence of such complications is unknown.

In the current study, we present the incidence and resultant morbidity and mortality associated with such complications during 8 years in a single high-referral pediatric institution, and we propose recommendations that might help to avoid such life-threatening complications. To the best of our knowledge, this is the largest series on this topic in the modern medical literature to date.

Methods

Study Population

The medical records of 437 patients who were admitted to Abo El-Reesh Children's Hospital with a diagnosis of posterior fossa tumor between January 2005 and December 2012 were retrospectively reviewed to evaluate the incidence, resultant morbidity and mortality, and predictive factors for the occurrence of ITH or UTH following placement of a precraniotomy VP shunt or ETV. All medical records and imaging studies were reviewed and analyzed. For all patients included in the study, preoperative CT and/or MRI with and without contrast and a post–CSF diversion CT scan without contrast were performed.

Operative Procedures

The decision to perform CSF diversion before resection was usually guided by the degree of hydrocephalus, the clinical state of the patient, the response to medical treatment (glucocorticosteroids and diuretics), and the expected waiting period before scheduling of definitive surgery for the tumor could be performed.

Corticosteroids and acetazolamide were given to most patients with hydrocephalus and posterior fossa tumors unless contraindicated. CSF diversion was planned if the clinical condition did not improve (such as persistent vomiting and headache) or in patients with significant hydrocephalus (common in our patients due to late presentation) who were scheduled for tumor resection after more than 10 days and discharged after CSF diversion. It is worth mentioning that due to limited hospital resources, most patients were discharged from the hospital on the 2nd day after CSF diversion and were asked to return 1 day prior to the scheduled day of definitive surgery.

Ventriculoperitoneal shunt placement was usually performed by residents the day following admission, except in patients presenting in a critically ill state with severe hydrocephalus; for these patients, a shunt was urgently implanted on the same day as admission. A medium-pressure VP shunt was implanted using the conventional technique (either right frontal or posterior parietal bur hole). Endoscopic third ventriculostomy was performed electively by a senior staff member, typically within 3 days of admission in patients with a more stable clinical condition. It is noteworthy that patients were often selected for ETV if they had a lower chance of requiring a postoperative VP shunt, such as closed-head children suffering from relatively smaller tumors located at the cerebellar hemisphere rather than the fourth ventricle. External ventricular drain insertion was avoided because of fear of infection.

Any changes in neurological status or development of new deficits following precraniotomy CSF diversion (using a shunt or ETV) were analyzed. The management of these complications and the final outcomes were also evaluated.

A diagnosis of ITH was made when the patient developed deterioration of neurological status following CSF diversion and a CT brain scan showed acute hemorrhage within the tumor (hyperdense areas). Upward transtentorial herniation was diagnosed when the patient demonstrated a disturbance of consciousness, the CT brain scan revealed obliteration of the quadrigeminal and ambient cisterns, and there was no other new evident pathology. The final outcomes of these complications upon discharge of the patient from the hospital were classified according to the Glasgow Outcome Scale, i.e., good recovery, moderate disability, severe disability, vegetative state, and deceased.

Statistical Analysis

Data were statistically described in terms of frequencies (number of cases) and percentages. Comparisons between the study groups were performed using the chi-square test. However, Yates's correction equation was used when the expected frequency was less than 5, and p values less than 0.05 were considered statistically significant. All statistical calculations were performed using the computer program SPSS for Windows (version 15, SPSS Inc.).

Results

A total of 437 patients were analyzed. The patient ages ranged from 1 month to 14.8 years, with a mean of 7.2 ± 3.6 years. There was a slight overall male predominance, with a male-to-female ratio of 182/155 (1.17).

The most common tumors were medulloblastomas.
(37.3%), followed by astrocytomas (37.1%) and ependymomas (14%). Hydrocephalus was noted in 381 patients, and 301 (79%) of these cases underwent CSF diversion before resection, while 80 (21%) with mild hydrocephalus responded well to medical treatment. A VP shunt was placed in 214 (71.1%) of these 301 patients, including 92 VP shunts inserted urgently on the same day of admission due to poor patient condition, while 87 patients (28.9%) underwent ETV. The mean time from admission to shunt placement was 1.3 days (range 0–4 days), while the mean time from admission to ETV was 3.1 days (range 1–5 days). The interval between CSF diversion and craniotomy ranged from 4 to 18 days (mean 10.4 days).

Following VP shunt placement, 181 (84.6%) of 214 patients showed improvement in the clinical symptoms of increased ICP, 27 patients (12.6%) showed no change after precraniotomy shunt placement, and 6 patients (2.8%) deteriorated neurologically. ETV was performed in 87 patients; of these, 60 (69%) showed improvement in the clinical signs of increased ICP, 26 patients (29.9%) showed no change, and 1 patient (1.1%) deteriorated. The difference in the incidence of infratentorial complications between a VP shunt and ETV was found to be statistically nonsignificant (p = 0.659). The data of 7 patients with infratentorial complications are listed in Table 1.

The ages of the 7 patients who deteriorated neurologically after CSF diversion ranged from 10 months to 14 years (average age 5 years). There was an evident male predominance (M/F ratio = 2.5/1). Most of the cases deteriorated within the first 8 hours after CSF diversion; 2 did not recover from anesthesia, and 1 deteriorated after 24 hours.

Five patients developed ITH (4 after VP shunt placement and 1 after ETV). Of the patients with VP shunts, 2 died before any neurosurgical intervention could be performed, 1 did not recover despite urgent tumor resection (Figs. 1–3), and the fourth child became vegetative after tumor excision and died 1 year later. The fifth patient who underwent ETV did not recover despite urgent tumor resection. Two patients developed UTH (after VP shunt placement); 1 deteriorated rapidly within 1 hour and became flat and apneic and died shortly thereafter, while the other patient deteriorated 24 hours after recovery from anesthesia. After urgent tumor excision, this patient recovered and was discharged from the hospital with only mild ataxia (Fig. 4).

Three patients died before tumor resection, and no pathology was available because the families refused postmortem examinations. Of the other 4 patients who underwent urgent tumor excision, 2 had medulloblastomas (50%), 1 had an astrocytoma (25%), and 1 had an ependymoma (25%).

Statistical analysis with the aim of determining predictive factors for the occurrence of ITH and UTH following CSF diversion was not possible, because to determine independent risk factors for these complications by logistic regression, a larger frequency of ITH and UTH cases was needed.

**Discussion**

Hydrocephalus is often the cause of the presenting signs and symptoms in patients with posterior fossa tumors. However, the perioperative management of hydrocephalus associated with posterior fossa tumors in children continues to be problematic. Preresection hydrocephalus can be managed either with an initial CSF diversion procedure such as ETV, VP shunting, or EVD followed by resection, or by directly addressing the obstructing posterior fossa tumor with primary resection at the earliest opportunity. Elkins and Fonseca in 1961 and Abraham and Chandy in 1963 advocated precraniotomy shunting in the management of children with posterior fossa tumors. The success of this approach was confirmed by others. However, in the new millennium, precraniotomy shunting has been practically abandoned in countries with abundant resources because of the associated shunt complications. Alternatively, “routine” ETV before craniotomy has been recommended for the management of hydrocephalus secondary to posterior fossa tumors. This technique reduced the necessity of implanting a permanent CSF shunt device from approximately 35% to only 6% of cases, with subsequent avoidance of many shunt-related complications.

More recently, the focus has shifted to primary resection, which directly addresses the obstructing posterior fossa tumor. The proponents of this approach have debated whether routine ETV is actually necessary because the low rate of persistent hydrocephalus does not justify adopting a routine preoperative procedure. However, such a new approach is difficult to apply at our institution.
because we have the same problem as other developing countries,17,30 i.e., a very high referral rate exceeding our tumor excision capacity. Therefore, there is a relatively long waiting list of children with posterior fossa tumors. Moreover, the diagnosis of children with posterior fossa tumors occurs relatively late, which results in very large tumors that frequently fill and protrude out of the fourth ventricle with resultant severe obstructive hydrocephalus.

Precraniotomy CSF diversion (shunting or less often ETV) is the most common approach used in our university hospital. Because of limited hospital resources, most patients are discharged from the hospital on the 2nd day after CSF diversion, while definitive resection is typically scheduled 1 to 2 weeks later. Of 381 children with hydrocephalus due to posterior fossa tumors, only 80 patients (21%) did not undergo CSF diversion before resection. Such patients responded well to medical treatment and were either lucky to find a hospital bed until their scheduled tumor resection or could be safely discharged from the hospital because they lived close to the hospital and their educated families were instructed to come back urgently in case of any clinical deterioration.

Following ventricular tapping, there is a sudden decrease in CSF pressure, which results in disturbance of the dynamic balance between the various intracranial contents and leads to an increase in the cerebral blood flow and vascular congestion.22 The mechanism of ITH is ascribed to the immaturity, fragility, and structural abnormality of tumor vessels. In malignant tumors such as medulloblastomas and glioblastomas, the new tumor vessels are thin-walled and are often weak and subject to disruption when stretched and distorted.42,44 Moreover, rapid decompression of the supratentorial ventricular system upsets the delicate balance of pressures between the supratentorial and infratentorial compartments, thus resulting in a significant pressure differential between the supratentorial and infratentorial compartments and leading to herniation of the midbrain and cerebellar vermis superiorly through the tentorial notch.20,45 The clinical symptoms of UTH have been described as hyperventilation, progressive obtundation, conjugate downward gaze, or loss of upward gaze.32 In particular, Rosenfeld noted that this complication is more likely to occur if there is already preoperative visual compromise such as sluggish or dilated pupils, afferent papillary defect, reduced visual acuity, or restricted visual fields.34

It is worth noting that ITH may lead to UTH due to accentuation of the pressure gradient between the supratentorial and infratentorial compartments (Fig. 2). The reverse is also true, as UTH may lead to ITH due to tumoral venous congestion after herniation of the posterior fossa contents through the tentorial notch, in the same mechanism as strangulated hernia in other organs. Thus, there is an overlapping relationship between these different pathologies.

It is clear that the pathological mechanisms leading to
ITH and UTH may occur after any ventricular tapping procedure such as VP shunt placement, EVD, and ETV. Although these complications have been rarely reported with ETV compared with VP shunt placement,16 there is actually greater potential for rapid CSF egress during the ETV procedure compared with passing a ventricular catheter. The current study confirms that ETV is not exempt from such complications, as 1 of our patients did not recover after ETV due to documented ITH. The incidence of infratentorial complications between VP shunt placement (6/214, 2.8%) and ETV (1/87, 1.1%) was not found to differ significantly (p = 0.659).

The actual incidence of these serious and mostly fatal infratentorial complications (ITH and/or UTH) is not accurately known because only case reports or small case series have been reported (Table 2).12,14,17,36,37,41,44 Epstein and Muralia17 reported that 3 (10%) of 30 patients developed ITH and/or UTH, and Hoffman et al.36 reported that 6 (6.3%) of 96 patients with posterior fossa tumors developed UTH after preresection shunt placement, although this high incidence may have been due to an old shunt design that allowed excessive and rapid lowering of CSF pressure.17 In contrast, a lower and more realistic incidence of infratentorial complications, in which all cases were classified as UTH only, following precraniotomy shunting was reported by Albright,3 Raimondi and Tomita32 (3% each), and Griwan et al.17 (1.6%).

In the current study of 437 children with posterior fossa tumors who were admitted to an Egyptian high-referral center over an 8-year period, 301 patients from a total of 381 with hydrocephalus underwent CSF diversion before resection. The incidence rate of infratentorial complications (ITH and UTH) of 2.3% (7/301), and these complications had a grave prognosis in most cases (85.7%). The incidence of ITH was 1.7% (5/301) with a 100% mortality rate, while the incidence of UTH was 0.7% (2/301) and the resultant mortality rate was significant (50%). Thus, the actual incidence of ITH was much more common than UTH, which is in contrast to most previous reports showing that the majority of cases presented with UTH,3,14,17,18,32,45 most likely due to limited CT resolution and unawareness of such pathology.

Regarding the clinical presentation, all of our 7 patients who developed infratentorial complications after CSF diversion showed severe symptoms and signs of intracranial hypertension (repeated vomiting and headache, and bilateral papilledema). Of these 7 patients, 5 had truncal ataxia (71.4%), 2 had abducent nerve palsy (28.6%), 2 had diminution of vision, and 1 had bulbar manifestations (14.3%). In a recent study conducted at our university hospital on 221 posterior fossa tumors,31 the incidence of intracranial hypertension, ataxia, abducent nerve palsy, diminution of vision, and bulbar manifestations was 83.3%, 33%, 14%, 10.9%, and 7.7% respectively. Compared with these results, the patients who developed infratentorial complications after CSF diversion had a higher incidence of severe hydrocephalus manifestations (intracranial hypertension, abducent nerve palsy, and diminution of vision) and a higher incidence of ataxia, which may be attributed to larger tumor sizes due to relatively late presentation.

Radiologically, CT scans before and after CSF diversion were obtained for all 7 patients in the current study.
TABLE 2. Published case reports of ITH and UTH (with sufficient data) after precraniotomy CSF diversion in children with posterior fossa tumors

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Incidence</th>
<th>Age, Sex</th>
<th>Preoperative Presentation</th>
<th>CT Result</th>
<th>Deterioration Time</th>
<th>Pathology</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein &amp; Murali, 1978</td>
<td>3</td>
<td>10%</td>
<td>9 yrs, F</td>
<td>Increased ICP, diplopia</td>
<td>ITH &amp; UTH</td>
<td>Immediate</td>
<td>Astrocytoma Grade I</td>
<td>Shunt, resection</td>
<td>Severe disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17 yrs, F</td>
<td>Increased ICP, ataxia, multiple cranial nerve palsies, (bilat) lower-limb spasticity</td>
<td>ITH &amp; UTH</td>
<td>Immediate</td>
<td>Astrocytoma Grade III</td>
<td>Shunt, resection</td>
<td>Death</td>
</tr>
<tr>
<td>Vaquero et al., 1981</td>
<td>1</td>
<td>NA</td>
<td>7 yrs, M</td>
<td>Increased ICP, rt CN VI palsy, &amp; truncal ataxia</td>
<td>ITH</td>
<td>8 hrs</td>
<td>Astrocytoma</td>
<td>EVD</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>Increased ICP, rt CN VI palsy, &amp; truncal ataxia</td>
<td>ITH</td>
<td>7 hrs</td>
<td>Medulloblastoma</td>
<td>EVD</td>
<td>Death</td>
</tr>
<tr>
<td>Waga et al., 1981</td>
<td>1</td>
<td>NA</td>
<td>11 yrs, M</td>
<td>Increased ICP, diplopia, nystagmus, ataxia</td>
<td>ITH</td>
<td>Immediate</td>
<td>Malignant astrocytoma</td>
<td>Shunt</td>
<td>Death</td>
</tr>
<tr>
<td>Zuccarello et al., 1985</td>
<td>1</td>
<td>NA</td>
<td>4 mos, M</td>
<td>Increased ICP</td>
<td>ITH &amp; UTH</td>
<td>2 hrs</td>
<td>Ependymoma</td>
<td>Shunt, resection</td>
<td>Death</td>
</tr>
<tr>
<td>Elgamal et al., 2006</td>
<td>1</td>
<td>NA</td>
<td>13 yrs, M</td>
<td>Increased ICP, lt CN VI palsy</td>
<td>ITH &amp; UTH</td>
<td>6 hrs</td>
<td>Medulloblastoma</td>
<td>EVD, resection</td>
<td>Death</td>
</tr>
<tr>
<td>Santhanam et al., 2009</td>
<td>1</td>
<td>NA</td>
<td>8 yrs, F</td>
<td>Increased ICP, ataxia</td>
<td>ITH</td>
<td>Early</td>
<td>Astrocytoma</td>
<td>Shunt, resection</td>
<td>Vegetative &amp; death</td>
</tr>
<tr>
<td>Present study</td>
<td>7</td>
<td>2.3%</td>
<td>5 M/2 F, range 10 mos to 14 yrs</td>
<td>All increased ICP, 5 ataxia, 2 lt CN VI palsy, 2 diminution of vision</td>
<td>5 ITH, 2 UTH</td>
<td>Immediate to 24 hrs</td>
<td>2 medulloblastomas, 1 ependymoma, 1 astrocytoma</td>
<td>6 VP shunts, 1 ETV</td>
<td>6 deaths, 1 good recovery</td>
</tr>
</tbody>
</table>

CN = cranial nerve; NA = not available.
who developed infratentorial complications, while MR images of the brain before diversion was obtained for only 3 patients because this procedure is usually conducted within 48 hours due to crowded waiting lists (Fig. 1). It is clear that after neurological deterioration post–CSF diversion, MRI is not performed to save time for urgent surgical intervention. The most common radiological characteristics of the 7 posterior fossa tumors were their relatively large size (diameter ≥ 4 cm), with severe hydrocephalus (subependymal permeation in 6 cases) and significant peritumoral edema (5 cases). Six tumors were located at the fourth ventricle (4 close to the tentorial incisura, including 2 cases of UTH), whereas only 1 tumor was located at the cerebellar hemisphere.

Astrocytomas (66.7%) and medulloblastomas (22.2%) represent the majority of the previously reported cases of ITH and/or UTH following preresection CSF diversion in children (Table 2). This may be due to the fact they are the most common pediatric posterior fossa tumors.11,13 This finding was confirmed by this study, in which 50% of the pathologically verified tumors were medulloblastomas, followed by astrocytomas (25%) and ependymomas (25%).

The reported timing of neurological deterioration after preresection CSF diversion in posterior fossa tumors in children ranged from immediate (no recovery after CSF diversion) to 1 week (occurred early, i.e., within 8 hours in most reported cases).12,14,17,36,37,40,41,45 This is consistent with our results, which indicated that most of our cases deteriorated within 8 hours (85.7%); in particular, 2 patients deteriorated immediately, whereas 1 patient, the only survivor, deteriorated after 24 hours.

There appears to be a correlation between late deterioration due to UTH (≥ 24 hours) following CSF diversion and good recovery after urgent tumor excision. One previously reported surviving patient with astrocytoma deteriorated 1 week after shunt insertion,14 and our surviving patient with medulloblastoma deteriorated after 24 hours and suffered from UTH. In summary, perioperative management of hydrocephalus in children with posterior fossa tumors continues to be problematic. The modern management strategies are either precraniotomy ETV rather than VP shunt placement (except in low-resources countries) or direct tumor resection. Each approach has its advantages and disadvantages. However, specific infratentorial complications such as ITH and/or UTH may occur after any preresection ventricular tapping procedure. ITH may lead to UTH, and the reverse is also true. Thus, both pathologies are overlapping and have a poor prognosis. The current study confirms that ETV is not exempt from such complications; thus, routinely performing ETV before resection is not justified. Therefore, the authors make the following recommendations. First, a short course of high-dose corticosteroids and diuretics should be administered unless contraindicated to decrease the edema around the tumor and partially restore patency of the obstructed CSF pathways. Thus, the necessity of precraniotomy CSF diversion is reduced. Second, precraniotomy CSF diversion (shunt placement or ETV) should not be performed “routinely” in patients with posterior fossa tumors. Third, there is a higher risk of infratentorial complications (ITH and UTH) following precraniotomy CSF diversion (either VP shunt placement or ETV) in patients with large posterior fossa tumors (diameters ≥ 4 cm) extending close to the tentorial incisura, especially in patients with severe hydrocephalus (subependymal permeation) and significant peritumoral edema; such high-risk patients should be treated with corticosteroids and diuretics, insertion of an external ventricular drain set at high pressure, or earlier definitive tumor resection rather than CSF diversion. And fourth, additional resources should be allocated to pediatric neurosurgery centers in developing countries to decrease the waiting time for children with posterior fossa tumors and allow primary resection.

Conclusions

Infratentorial complications (ITH and UTH) are not uncommon after preresection CSF diversion such as VP shunt placement, EVD, or ETV, and are associated with a very poor prognosis in most cases, even with surgical interference.

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References


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