RESEARCH ARTICLE

Effect of Epanutin in Controlling fits in Paediatric Patients with Posterior Fossa Ependymoma

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ABSTRACT

Aim: The purpose of this study is to discuss efficacy of epanutin in controlling fits in patients with posterios fossa ependymoma in paediatric patients and the surgical removal of posterior fossa ependymoma tumour, focusing on the extent of the surgery and the resulting outcomes.

Materials And Methods: From January 2022 to December 2023, a total of 10 children diagnosed with fourth ventricular ependymoma underwent surgery using the telovelar technique. An assessment was conducted to determine the extent of radicality, neurological result, comorbidities, and survival rates. A statistical analysis was conducted to assess the ameliorative impact of epanutin in controlling convulsions in patients with posterios fossa ependymoma in paediatric patients.

Results: Complete excision of the tumor was successfully accomplished in 8 individuals, representing 80% of the total. Every patient necessitated the diversion of cerebrospinal fluid (CSF) by means of a ventriculoperitoneal shunt. One patient (10%) experienced cerebellar mutism, one patient (10%) experienced bulbar paralysis (lower cranial nerve palsy), and 3 patients (30%) exhibited tumor recurrence. Subtotal resection (p=0.020) and anaplastic ependymoma (p=0.038) were shown to be linked with a poor prognosis, as indicated by overall and progression-free survival rates. Moreover, twelve patients showed convulsions in postoperative period and epanutin was used in these patients and controlled fits in 75% of these patients.

Conclusion: The telovelar technique offers a sufficient anatomical view of the fourth ventricle and enables early observation and safeguarding of its floor (brainstem). It promotes sufficient thoroughness and is linked to a reduced occurrence of cerebellar mutism and other issues related to the method. Removing the posterior arch of the atlas can enhance the working angle, especially towards the front section of the fourth ventricle. Epanutin is effective in controlling convulsions in patients with posterior fossa ependymoma.

Keywords: Epanutin, Paediatric, Fourth ventricle, Posterior fossa, Telovelar approach, Cerebellar mutism.

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INTRODUCTION

Contemporary approaches to epilepsy treatment aim to manage seizures effectively while reducing or eliminating the underlying cerebral dysrhythmia. Epanutin, a phenytoin sodium, is a medication in the management and treatment of epilepsy, including generalized tonic-clonic seizures, complex partial seizures, and status epilepticus. It belongs to the class of anticonvulsants. This activity delineates the indications, mechanism of action, and contraindications for phenytoin as a vital therapeutic agent in epilepsy treatment (1).The fourth ventricle is tough to reach due to its direct connection to the brainstem and its deep placement in front of and below the cerebellum (24). Performing the transvermian approach to the fourth ventricle by splitting the inferior vermis can lead to the development of caudal vermis syndrome, cerebellar mutism, or damage to the dentate nuclei, resulting in symptoms such as head nodding, truncal ataxia, and nystagmus (2,11,21,30).The telovelar technique is considered the preferred method for treating the majority of fourth ventricle lesions. Nevertheless, the current clinical series that discuss the advantages and disadvantages of this strategy lack sufficient data to thoroughly assess the outcome (26).

MATERIAL and METHODS

This study involved 10 male and female patients who had just been diagnosed with a fourth ventricle tumour. Two of the patients were admitted to 57357 Children Cancer Hospital, Egypt. The rest of the patients were admitted to Minia University Hospital, Egypt, from January 2022 to December 2023. Patients who had lesions just in the cerebellum or cerebellopontine angle, as well as those with recurring or residual lesions, were not included. Written informed consent was obtained from all legal guardians of the patients. The patients underwent preoperative imaging,

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Table 1: Clinical, Demographic and Surgical Data of Study Cases

Characteristic	No. of patients n (%)
Age (years): Mean; 6.05 (range 2 to 15)	
<5 years	4 (40)
5-18 years	6 (60)
Gender	6M/4F
Tumor Size	
<5 cm	4 (40)
>5cm	6 (60)
Tumor location	
With V4 floor infiltration	6 (60)
Without V4 floor infiltration	4 (40)
Extent of tumor resection	
GTR	8 (80)
STR	2 (20)
Pathological subtypes	
Ependymoma GII	8 (80)
Anaplastic ependymoma GIII	2 (20)

F: Female, GTR: gross total resection, M: Male, STR: subtotal resection, V4: fourth ventricle.

Table 2: Clinical Data of Study Cases

Charactristic	No. of patients (%)
Presenting Symptoms and Signs	
Hydrocephalus	10 (100.0)
Headache & Crying	9 (90)
Abnormal gait	8 (80)
Vomiting	7 (70)
Papilledema	6 (60)
Blurring of Vision	7 (70)
Diplopia	3 (30)
Cranial nerve palsy	2 (20)
Head tilt	2 (20)
Bulbar symptom	1 (10)
Ataxia	5 (50)
Mainly encountered postoperative complications	
Neck pain	4 (40)
Psedomeningocele	3 (30)
CSF infection	2 (20)
Cerebellar Mutism	1 (10)
Bulbar palsy	2 (20)
Subdural collection	1 (10)
Fits	9 (75%)

including computed tomography (CT) and magnetic resonance imaging (MRI), to evaluate their ventricular size and diagnose hydrocephalus. Every patient exhibited obstructive hydrocephalus, for which ventriculoperitoneal (VP) shunts were surgically implanted.

In all patients, prior to elevating the occipital bone flap, a standard procedure was carried out to remove the posterior arch of the atlas, approximately 1 cm away from the midline on both sides. The telovelar technique was executed by dissecting the arachnoid membrane on both sides along the tonsillomedullary and uvulotonsillar fissures. This allowed for the separation and safer retraction of the cerebellar tonsils, effectively releasing them. By performing a precise dissection, the tela choroidea was accessed and subsequently opened. Following this, the inferior medullary velum was incised. Performing these steps on both sides gives for extensive access to the entire fourth ventricle and complete removal of the tumor. In case of huge tumors, the initial step involved is central debulking. The tonsils were elevated slightly using retractors. The early detection of the boundary between the tumor and the brainstem allowed for the safeguarding of the brainstem using a cottonoid. The main objective of the surgery was to completely remove the tumor, except in situations where the tumor had invaded the brainstem, in which a thin layer of the tumor was left on the floor of the ventricle without entering the brainstem. By flexing the head and removing the arch of the atlas, the full length of the ventricular floor up to the Sylvian aqueduct was exposed. After the surgery, all patients were given a thorough neurological examination, focusing on conditions related to the back half of the brain. Specifically, the examination aimed to determine whether the patients had a total or partial cerebellar mutism syndrome and identify the specific aspects affected, such as language, neuro-behavioral functions, and/or motor skills. In addition, the examination evaluated any instances of delayed cerebrospinal fluid (CSF) accumulation and CSF leakage as well as fits. All patients underwent a non-contrast CT scan of the brain within 24 hours of the operation to rule out the presence of hematoma and substantial pneumocephalus, as well as to evaluate the size of the ventricles. A brain MRI was conducted within 48 hours to assess the degree of tumor removal. During the follow-up period, MRI scans of the brain and spine were conducted every 3 months in the first year and every 6 months afterwards. These scans were done with and without contrast to identify any potential tumor recurrence or spread of cancer cells in the CSF.Twelve patients had fits postoperative and epanutin was added to their treatment to control the fits.All patients underwent histopathological analysis of the biopsy material and were graded according to the WHO criteria. Cytological analysis was conducted on CSF samples collected at least 2 weeks after the surgery to evaluate the presence of CSF spreading.All patients were administered adjuvant radiotherapy based on their histological diagnosis.The assessment of the outcome was conducted

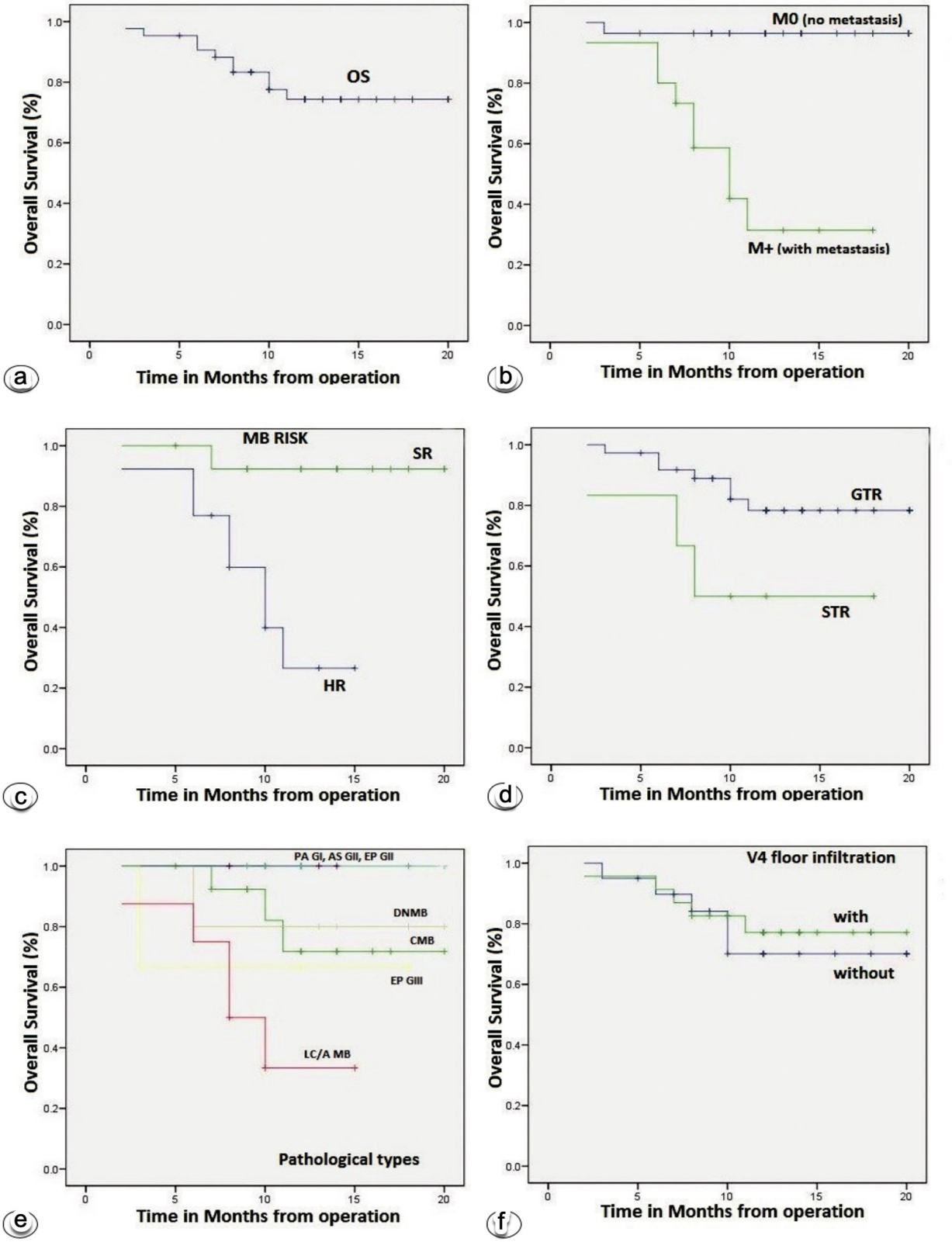

Figure 1: Kaplan–Meier estimation for OS based on clinical factors: a:OS in all cases; b: CSF seeding of tumor (M0 versus M+); c: HR group of MB versus SR group; d:GTR versus STR; e: Pathological subtypes; f: Tumor location with V4 floor infiltration versus without infiltration

in all patients at specific intervals: immediately after the operation, upon discharge, 3 weeks after the operation, and subsequently every 3 months.The statistical analysis was conducted using the SPSS program developed by SPSS Inc., based in Chicago, IL, USA. Overall survival (OS) refers to the period of time, measured in months, from the

removal of the tumor to the final follow-up or death. Progression-free survival (PFS) refers to the period of time, measured in months, from the removal of the tumor until the occurrence of the first relapse at any location, the final follow-up, or death.The prognostic value of the following factors was assessed: age (categorized as <5 years or 5–12 years), gender, metastatic stage (classified as M0 or M+), extent of resection (categorized as gross tumor resection [GTR] or subtotal tumor resection [STR]), pathological type, tumor site (with or without infiltration of the fourth ventricle floor), and tumor size (categorized as <5 cm or >5 cm in maximal diameter). Kaplan-Meier statistics were used to perform survival analysis for the several outcome parameters, including PFS and OS, through univariate analysis. The Cox multivariate regression analysis was employed to ascertain the impact of significant factors on OS and PFS. A p-value less than 0.05 was deemed to be statistically significant.

RESULTS

Characteristics of the patients

Table I shows that there were 6 male patients and 4 female patients, with a male-to-female ratio of 1.5:1. Table II lists the main symptoms and signs observed in these patients.There was no notable disparity in PFS between patients aged 5-12 years and those under 5 years old (2-year PFS rates of 70.6% and 62.7% respectively, p=0.508) (Table III).

Tumor Characteristics

The tumors were categorized based on their size, specifically their maximum diameter measured in centimeters. They were divided into two groups: tumors with a diameter less than 5 cm and tumors with a diameter greater than 5 cm, as indicated in Table I.

Localization and Scope of Tumor Removal

The tumor's location was determined based on preoperative imaging and surgical reports. The tumors were categorized into two subgroups (Table I). The initial subtype consisted of tumors that exhibited infiltration of the fourth ventricle (V4) floor, specifically attaching to the brain stem. The subsequent subtype consisted of tumors that did not exhibit infiltration of the V4 floor. There was no statistically significant difference in result between the two groups, as indicated by the p-values of 0.947 for PFS and 0.690 for OS. Gross total resection (GTR) was defined as either a tumor residual measuring less than 1.5 cm2 in the postoperative MRI, the absence of any visible tumor remaining, or the presence of only a thin layer of tumor left on the brain stem. Out of the 6 patients whose tumors were discovered to penetrate or be connected to the brainstem, complete tumor resection (GTR) was successfully performed in 4 individuals, with a success rate of 66.6%. In 33.3% of the remaining patients, sub-total resection (STR) was conducted due to the tumor being attached to or invading the brainstem, which impeded complete resection (Table I). Patients who underwent gross total resection (GTR) had a significantly superior prognosis compared to those who underwent subtotal resection (STR), with a 2-year progression-free survival (PFS) rate of 93.3% versus 18.7% respectively (p=0.020)

Histopathological Types

The study's Table I provides a summary of the different pathological subtypes of tumors. Among them, patients with ependymoma (EP) GII showed no progression throughout the follow-up period and achieved the most favorable outcome, with a 2-year progression-free survival (PFS) rate of 100.0%. Patients diagnosed with EP Grade III (GIII) had the most unfavorable prognosis, with a 2-year progression-free survival (PFS) rate of 33.3%.

Postoperative Complications

The primary complications observed after surgery, listed in descending order of occurrence, included neck pain, pseudomeningocele, CSF infection, cerebellar mutism, bulbar palsy, and subdural collection (Table II).Two patients (20%) experienced a CSF infection. The patients underwent shunt removal and external ventricular drain insertion to address the infection, after which a new VP shunt was inserted. A single patient had the development of severe ventriculitis and septicemia, ultimately resulting in death.One patient (10%) experienced bilateral subdural fluid collection, necessitating the evacuation of the fluid and the upgrading of their medium pressure ventriculoperitoneal (VP) shunts to high pressure shunts. Twelve patients (60%) had postoperative fits and epanutin was added to their treatment protocol. Epanutin showed satisfactory outcomes in controlling the fits in nine of these patients (75%).

Analysis of Cerebellar Mutism

One patient (10%) experienced cerebellar mutism (CM) with grade III EP. The mutism began between 2 and 3 days after the surgery, with an average onset of 2.50 ± 0.548 days.This patient exhibited mild to moderate mutism, accompanied by reduced verbal expression, hypotonia, and oropharyngeal dysfunction, resulting in dysphagia and decreased oral consumption. There was a progressive and spontaneous improvement within 2-6 months after the surgery, but the patient still had some remaining dysarthria.

Analysis of Bulbar Palsy postoperatively

One patient (10%) experienced bulbar symptoms before the surgery, and one patient (10%) developed new-onset bulbar symptoms after the surgery. These two patients had EP GIII. One of them experienced mild to moderate asphyxiation, which eventually ameliorated within a span of one month. The other underwent tracheostomy, which was terminated after a period of 2-4 months.

Outcomes

Tumor recurrence was observed in 1 patient, accounting for 10% of the cases. This patient had EP GIII tumors, with recurrences occurring 6 months.Disease progression: None of the patients with EP GII experienced any progression throughout the follow-up period, resulting in the most favorable overall outcome. Out of the two patients with EP GIII, one had tumor recurrence during the follow-up period.Out of the total number of patients, 1 individual (10%) passed away throughout the course of the study. He experienced tumor recurrence and eventually died.

DISCUSSION

In 1922, Matsushima et al. were the first to illustrate the structure of the cerebellomedullary fissure. They proposed that this fissure could be used as a possible pathway to access the fourth ventricle without causing damage to brain tissue (16). Among the 10 patients in our study, 8 patients (80%) achieved gross total resection (GTR), while 2 patients (20%) achieved subtotal resection (STR). The main cause of STR was primarily related to the involvement of the brainstem. In general, we encountered no issues regarding the size or position of the tumor in the superior region of the ventricle. The GTR (Gross Total Resection) rate was 88.9% in the case series conducted by Tomasello et al. (25,26), and 82.0% in the series conducted by Han et al. (10).Our investigation revealed that larger tumors have a tendency to elongate and reduce the thickness of the inferior medullary velum and tela choroidea. This alteration facilitates easier and broader access to the tumor, allowing for early access to the ventricle floor. Tomasello et al. (25,26) also reported the same.Brainstem involvement was found to be a significant factor related with STR (p=0.008) in 60% of the 6 individuals whose tumors were invading or connected to the brainstem in our dataset. Gross total resection (GTR), which refers to either completely removing the tumor or leaving a very thin layer on the brain stem to prevent damage, was successfully done in 8 patients (80%), while the remaining 2 patients (20%) had subtotal resection (STR). Nevertheless, this issue might also arise while using the transvermian route. The findings suggest that tumor attachment to the brainstem does not completely prevent the complete removal of the tumor, which aligns with the findings of Winkler et al.'s study (28).Tomasello et al. also found that big tumors and tumors that reach the upper third of the fourth ventricle pose greater surgical difficulties and increase the likelihood of both subtotal resection (STR) and postoperative hydrocephalus (requiring a shunt) (25,26). Difficulties may also arise while selecting the transvermian path, as documented by Tanriover et al.The transvermian method offers a greater range of motion for accessing the front half of the fourth ventricle compared to the telovelar approach (24). In contrast, we did not see any issues with GTR of tumors that spread to the rostral third of the fourth ventricle. This is because we regularly remove the posterior arch of the atlas, which allows for a broader range of movement during the procedure. Deshmukh et al. have concluded that the telovelar method, combined with the removal of the posterior arch of the atlas, provides a larger working angle to the upper third of the ventricle compared to the angle afforded by the transvermian approach (4). Surgical removal of sections of the cerebellar tonsils has been suggested as a remedy for the constraints of the telovelar approach in cases where the tumor is large or spreads upwards and sideways (14). Nevertheless, we maintain that excision of the tonsils is not crucial in these instances.The telovelar technique offers the benefit of early imaging and dissection of the interface between the tumor and the floor of the fourth ventricle, unlike the transvermian approach, which accesses the tumor from the posterior side. The prevalence of CM in our study was 10%. According to reports, the telovelar method can result in a CM rate as high as 30% (10,29).Gok et al., Han et al., and Matsushima et al. found that all cases of CM had experienced bilateral telovelar opening, but the likelihood of CM occurring with unilateral telovelar opening was unlikely (9,10,17). In contrast, Tomasello et al. employed bilateral fissure opening and did not encounter any cases of CM (25,26).They suggested that the absence of CM in their study could be attributed to the comparatively higher average age of their patients. Additionally, they proposed that the risk of cerebellar dysfunction could be mitigated by increasing the width of the fissure opening and minimizing the extent of cerebellar retraction. For our research, we employed bilateral fissure opening and careful retraction in nearly all instances. However, we encountered one case (10%) of CM. Thus, we can only conjecture about the etiology of CM in this patient. It could be linked to the young average age of our patients (6.05 years) and/or the temporary swelling of the cerebellum and dentate nuclei after surgery due to surgical manipulation or retraction of the cerebellum. Wells et al. also observed a notable swelling of the cerebellum and the middle and superior cerebellar peduncles in the postoperative scans of patients with CM (27). In our research, we observed that CM occurred between 48 and 96 hours after surgery. We found that patients who experienced CM also had residual dysarthria, a condition that had been previously described as the syndrome of CM with subsequent dysarthria (5). This patient in our study who had CM exhibited a pathology of EP GIII.Our analysis revealed a notable increase in the likelihood of bulbar paralysis in individuals who had received subtotal resection (STR) compared to those who had undergone gross total resection (GTR) (p=0.034). This heightened risk may be attributed to brainstem invasion rather than the STR procedure itself. The estimated 2-year progression-free survival (PFS) and overall survival (OS) rates for all patients in our series were 68.1% ± 7.4% (15.632 months) and 74.3% ± 7.1% (16.755 months), respectively. Compared to Jiang et al., who reported a 5-year progression-free survival (PFS) rate of 47.1% ± 4.6% and an overall survival (OS) rate of 54.6% ± 4.6%, this is a comparatively superior outcome (13).Our study found that individuals diagnosed with ependymoma GII did not experience any disease progression throughout the follow-up period, resulting in the most favorable overall outcome. Patients diagnosed with EP GIII had the most unfavorable prognosis. These findings align with the results of other clinical studies (6,8), which have indicated that MB and EP GIII have the poorest prognosis compared to other malignancies in the posterior fossa. Jiang et al. conducted a study on three types of brain tumors: CMB, DNMB, and LC/A MB. They reported a 5-year progression-free survival (PFS) rate of 51.4% for CMB, 50.0% for DNMB, and 9.1% for LC/A MB (13).The initial prognosis of patients is directly linked to the surgical operation and the subsequent complications, whereas the long-term prognosis is influenced by other factors such as disease-

related complications and the delayed impact of additional treatments, as mentioned in other studies (12).Posterior fossa ependymoma has been categorized into three molecular subtypes. The types of this condition are sub-ependymoma (PF-SE), PF-EPN-A, and PF-EPN-B (1). Although these molecular subgroups have comparable histological characteristics, they exhibit differential behavior and prognosis. Therefore, we strongly advise doing prospective study to differentiates between these molecular subgroups to increase the awareness regarding the competency of our findings.

CONCLUSION

The telovelar method has several advantages and leads to lower rates of complications compared to the transvermian procedure. Consequently, it should be the customary method for dealing with fourth ventricle abnormalities. If feasible, it is advantageous to get early access to the interface between the tumor and the floor of the fourth ventricle, as this promotes a safer removal of the tumor. If the tumor is attached to the floor of the ventricle, it is advisable to remove it while leaving a thin layer on the brainstem to prevent any damage to the brainstem. The wide aperture of the cerebellomedullary space ensures optimal visibility of the fourth ventricle chamber, including the lateral and superolateral recesses. This eliminates the need for extensive retraction of the tonsils. This approach leads to a reduced risk of CM and other dysfunctions of the cerebellum. We suggest regularly removing the posterior arch of the atlas to increase the working angle, especially towards the deep rostral region of the ventricle. Statistically significant negative prognostic variables include STR and anaplastic ependymoma GIII. Furthermore, Epanutin administration demonstrated satisfactory outcomes in controlling the fits in paediatric patients with posterior fossa ependymoma

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