

Complications Following Resection of Midline Posterior Fossa Tumors in Children

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ABSTRACT

Introduction: The midline posterior fossa is a common site of origin of brain tumors in children. The midline posterior fossa comprises critical neural structures like the floor of the fourth ventricle and vermis. Injury to any of these structures can result in a myriad of complications. In this study, we investigated the complications of surgery of posterior fossa tumors in children treated at our hospital to determine their predicting factors.

Methods: A retrospective review was carried out to explore the complications of surgery of posterior fossa tumors. A total of 246 children who had undergone surgery for posterior fossa tumors between 1st Jan 2006 and 31st Dec 2016 were considered for this study. A Chi-square test was done to check the association of complications with various factors. Binary logistic regression was performed to predict the occurrence of complications of surgical procedures and also to determine the predictive factors of each of the complications.

Results: Of the 246 children studied, 71(29%) had at least one neurological complication. The complications were classified as general and neurological; general complications included cerebrospinal fluid (CSF) infection, postoperative hematoma requiring evacuation, pseudomeningocele, pneumocephalus, fever; and neurological complications included cranial nerve deficits, long tract signs, and cerebellar dysfunction. Among the cranial nerve palsy, the commonest were 6th and 7th nerve palsy. Cerebellar mutism was noted in 9(3.7%) of the children. Other complications were twelfth nerve palsy, ataxia, limb weakness, headache and vomiting, fever, poor surgical wound healing, CSF leak, pseudomeningocele, and subdural hygroma. A Chi-square test was done to check the association of complication with various factors of which only post-operative impairment scale was found to be associated ($\chi^2=4.97$, p-value=0.035). The odds of complication for near-total resection were 1.94 times more than that of total resection, which was statistically significant (p-value = 0.04). For patients who had undergone shunt preoperatively, the odds of a complication were 53% less than those who had not. When each type of complication was analyzed individually, age below three years and extension beyond midline/spinal seeding were significant predictors of pneumocephalus, and subtotal resection was a significant predictor of gaze palsy.

Conclusion: Complications were not infrequent after surgery for midline posterior fossa in children. The extent of resection and pre-operative shunt were the main determinants of complications. Younger age and extension beyond midline/spinal seeding were contributory factors for pneumocephalus and subtotal resection a contributory factor for gaze palsy.

Keywords: midline posterior fossa, complications, posterior fossa syndrome, pneumocephalus, gaze palsy.

JMS: 2021; 24(1):28-35 DOI: <https://doi.org/10.33883/jms.v24i1.825>

INTRODUCTION

The midline posterior fossa is a common site of origin of brain tumors in children. The two most common tumors in this location are medulloblastomas and ependymomas. As per WHO 2007 classification, medulloblastoma is described as a tumor of a grade IV lesion and ependymomas are among tumors of neuroepithelial lesions¹. As per Collaborative Ependymoma Research Network (cern) foundation, approximately 1,340 ependymomas and ependymoma variants are diagnosed per year². The critical neural structures in the midline posterior fossa are the floor of the fourth ventricle and cerebellar vermis³. The floor of

the fourth ventricle contains nuclei of cranial nerves from the 6th to 12th and long tracts from the brain and cerebellum to the spinal cord. It also includes a center for critical functions like breathing and heart activity. The function of the cerebellar vermis is not restricted to motor control, and its damage during surgery can result in a myriad of complications, which is now known as posterior fossa syndrome. This syndrome comprises a triad of⁴ decreased speech production or mutism,² cerebellar dysfunction like

Access this article online



Website:
www.jmsskims.org

DOI:
<https://doi.org/10.33883/jms.v24i1.825>

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How to cite this article: Jayan M, Shukla DP, Palaniyappan M, Bhaskarapillai B, B ID. Complications Following Resection of Midline Posterior Fossa Tumors in Children. JMS 2021;24(1):28-35

Received: 2021-02-18 Accepted: 2021-04-01



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ataxia and axial hypotonia, and³ neurobehavioral affective symptoms such as irritability, emotional lability, and apathy^{4,5}. By virtue of the proximity of midline posterior fossa tumors to these critical neural structures, surgery of these tumors can result in potential complications. We analyzed complications of surgery of posterior fossa tumors in children treated at our hospital, intending to identify the factors affecting them.

MATERIALS AND METHODS

The present study is an observational study of complications of surgery of posterior fossa tumors. A retrospective review of the clinical case file and imaging of children who underwent surgery for midline posterior fossa tumors between 1st Jan 2006 and 31st Dec 2016 was done. The inclusion criteria were children aged 16 years or less, and first-time surgical resection of midline posterior fossa tumors, either ependymoma or medulloblastoma. The exclusion criteria were tumors in a location other than midline posterior fossa, histopathology other than ependymoma or medulloblastoma, and surgery other than resection of the tumor, viz, shunt, external ventricular drainage, re-exploration for recurrent tumor, etc.

The demographic characteristics like age and gender along with the clinical details like pre-operative neurological deficits, pre-operative neurological impairment scale dichotomized into bed-bound or ambulatory, pre-operative ventriculoperitoneal shunt for hydrocephalus, and extent of the tumor. The extent of resection based on the surgeon's judgment or postoperative CT scan was recorded. As MRI was not done for many children after surgery, the subtotal resection and partial resection were clubbed together for analysis purposes. The complications were classified as general and neurological; General complications included cerebrospinal fluid (CSF) infection, postoperative hematoma requiring evacuation, pseudomeningocele, pneumocephalus, and fever; and neurological complications, included cranial nerve deficits, long tract signs, and cerebellar dysfunction. The neurological complication was defined as the appearance of new neurological deficits after surgery or significant worsening of preexisting neurological deficits.

Statistical analysis

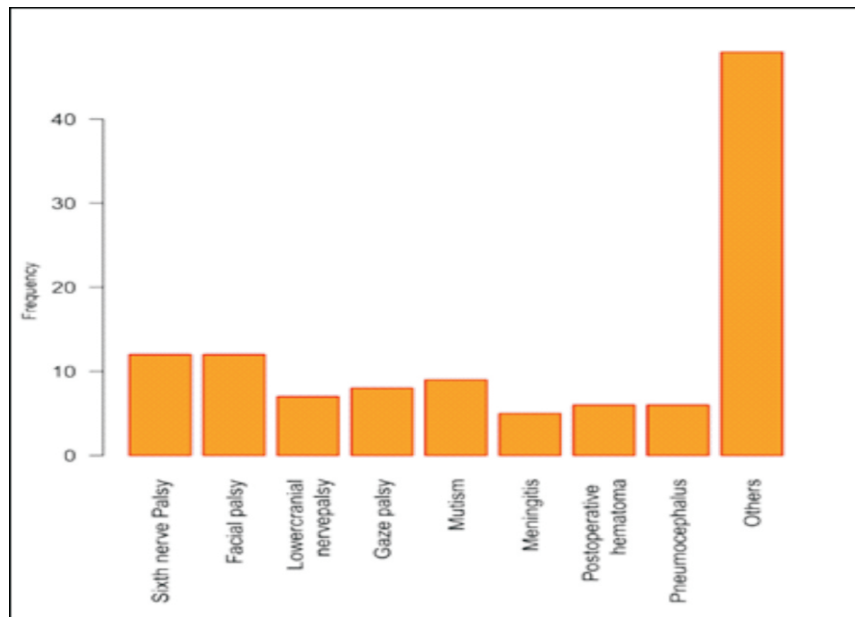
The mean and median time of survival showed no significant difference in patients with and without

complications. A Chi-square test was done to check the association of complication with various factors of which only post-operative impairment scale was found to be associated ($\chi^2=4.97$, p-value=0.035). Multiple logistic regression was performed to find out the significant predictors of complications of surgical procedure. Based on the clinical knowledge the covariates selected were age, histopathology, pre-operative shunt, hydrocephalus, the extent of resection, pre-operative neurological impairment scale, and extension of tumor beyond midline/spinal seeding. A receiver operating characteristic (ROC) curve was plotted for the model. Since the type of complications were more in number and the number of patients with each complication was not large enough, a separate analysis was conducted on selected types of complications to determine their predictive factors. This was done by creating a dummy variable for each complication, wherein the presence of that specific complication was coded as '1' and other complications, as well as no complications, were coded as '0'. Multiple logistic regression was conducted on each type of complication to determine their predictive factors. Risk estimates of odds ratio (OR) and 95% confidence intervals (95%CI) were reported. Further, the predictive ability of the fitted model was assessed using the area under the receiver operating characteristic curve (AUROC). All analysis was done using R version 3.6.1, Rcmdr version 2.6-2, with the help of *survival*, *glm2*, and *nnet* packages.

RESULTS

Of the two hundred forty-six children who had undergone surgical resection of midline posterior fossa tumor, 46(18.7%) were below three years and 76(30.9%) were female. The extent of resection was gross total in 105(42.5%), near-total 94(38.3%), subtotal 25(10%) and partial 23 (9.2%). Altogether 113(47%) had complications, of which 71(29%) children developed one of the neurological complications. The details of the complications are shown in Figure 1. Among the cranial nerve palsy, the commonest were 6th and 7th nerve palsy. Cerebellar mutism was noted in 9(3.7%) of children. Other complications were twelfth nerve palsy, ataxia, limb weakness, headache and vomiting, fever, poor surgical wound healing, CSF leak, pseudomeningocele, and subdural hygroma.

Fig. 1. Distribution of Complications Following Resection of Posterior Fossa Tumors.



The result of the binary logistic regression obtained for the presence of complications is given in Table 1. The odds of complication for near-total resection were 1.94 times more than total resection, which was statistically significant (p -value = 0.04), and that for subtotal resection were 1.77 times more as compared to total resection, but not statistically significant. Complications were 53% less for children who had shunt before surgery. Age categorized as 3 years and 3 years did not contribute to the presence of complications. Other variables not significant were histopathology, CT cyst, and extension beyond midline/spinal seeding.

The area under the ROC curve (AUROC curve) was 0.64

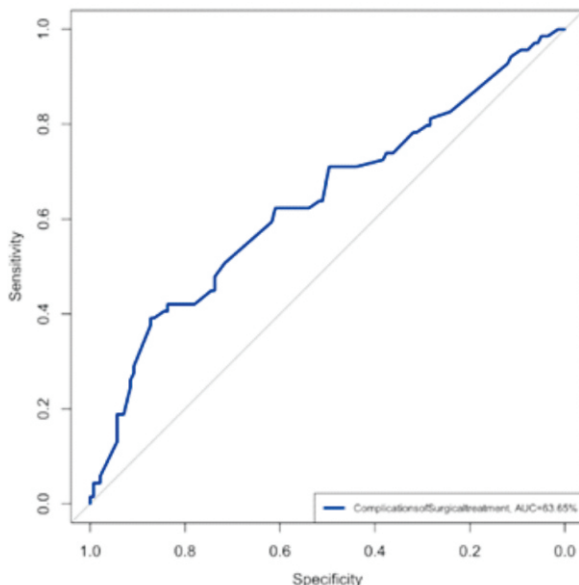
(95% CI: 0.56 - 0.72) which says that the predictive power of the model to discriminate the occurrence of complication and the non-occurrence was only 64.4% (shown in Fig. 2). When analyzed individually, age below three years and extension beyond midline/spinal seeding turned out to be significant predictors of pneumocephalus and the results are given in the appendices (Table 4). However, in multivariable analysis, the odds for pneumocephalus were 14 times more for children below 3 years (OR = 13.8, 95% CI: 1.39-137, p -value = 0.025) and 12 times more for those with extension beyond midline/spinal seeding (O.R = 11.8, 95% CI: 1.03-135, p -value = 0.048) (Table 2). Subtotal

Table. 1: Logistic Regression for the presence of Complication (n=246).

		Univariate analysis			Multivariable analysis		
		OR	95% CI	P value	OR	95% CI	P value
Age (years)	≤ 3 yr	0.76	0.36-1.59	0.46	0.63	0.27-1.49	0.29
Sex	Female	1.57	0.88-2.8	0.13	1.36	0.72-2.55	0.34
Shunt done preoperatively	Yes	0.52	0.27-1.03	0.06	0.47	0.23-0.95	0.04
Pre-operative neurological impairment status	Bed bound	1.74	0.45-6.7	0.42	2.97	0.65-13.60	0.16
Extent of Resection	Near total resection	1.74	0.95-3.17	0.07	1.94	1.02-3.66	0.04
	Subtotal resection	1.13	0.43-3.02	0.80	1.77	0.62-5.06	0.29

resection increased the odds for gaze palsy by nine times (OR = 8.65, 95% CI: 1.34-55.6, p-value = 0.023) compared to total resection, whereas near-total resection did not show any significance (Table 3). The AUC for these models were better when compared to the initial complication model, with AUC 0.91 (95% CI: 0.8-1.0) for pneumocephalus and 0.86 (95% CI: 0.76-0.95) for gaze palsy. The comparison of ROC curves of models for complications, pneumocephalus, and gaze palsy is shown in Figure 3. Other neurological complications were also analyzed individually, but none could be significantly predicted using any of the factors considered. The ROC curve for these analyses is shown in Figure 4 in the appendix and the odds ratio comparison in appendices (Table 5, 6).

Fig. 2. ROC Curve for Complications.



DISCUSSION

The occurrence of complications after surgery for midline posterior fossa tumors in children is not rare. Postoperative neurological sequelae are frequently observed in these children^{3, 6}. We analyzed the complication rate, type of complications, and predictors of complications following surgery for midline posterior fossa tumors in children. A relatively higher rate of complications as compared to what has been reported in the literature was observed^{3,6}. As we have included other complications, which are usually not mentioned in the literature, like postoperative hematoma, pneumocephalus, headache and vomiting, fever, poor surgical wound healing, CSF leak, pseudomeningocele, and subdural hygroma the incidence of complications

Fig. 3. Comparison of ROC Curves for Complications, Pneumocephalus, and Gaze Palsy.

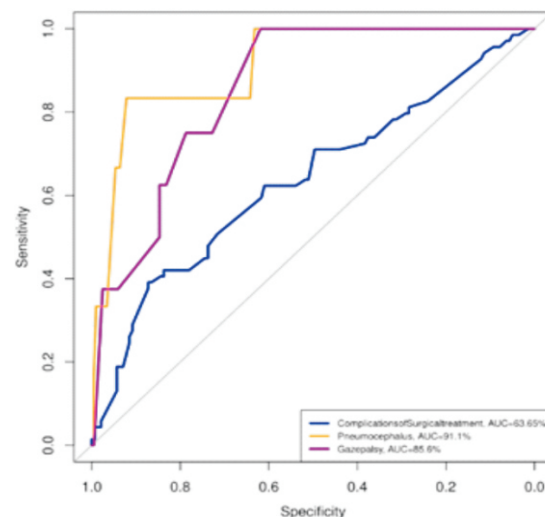


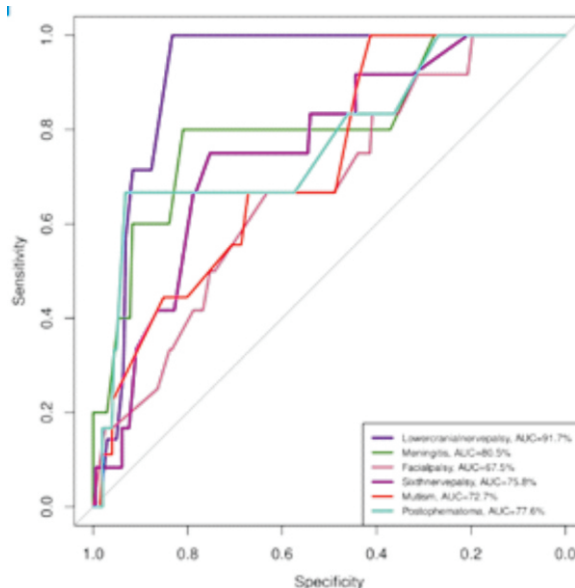
Table. 2: Multivariable Logistic Regression for Pneumocephalus.

		OR	95% CI	P value
Age (years)	≤ 3 yr	13.80	1.39-137	0.03
Extension and Spinal Seeding	At least one present	11.80	1.03-135	0.05

Table. 3: Multivariable Logistic Regression for Gaze Palsy.

		OR	95% CI	P value
Extent of Resection	Near total resection	1.69	0.28-10.3	0.57
	Subtotal resection	8.65	1.34-55.6	0.02

Fig. 4. Comparison of ROC curves for Lower cranial nerve palsy, Meningitis, Face Palsy, Sixth Nerve Palsy, Mutism, and Post-op Hematoma.



appears higher in our series. Moussalem et al., in their study of, complications in post-operative posterior fossa tumor in children, highlighted CSF leak transient cerebellar mutism, and hydrocephalus as the main issues⁶. Minor complications like vomiting, disequilibrium, headache, focal weakness, cranial nerve palsy, and fatigue were evaluated based on descriptive analysis⁶. Their study groups were defined based on their age, gender, and tumor histology. They had subjects up to 18yrs of age, whereas in our study group we had children aged only up to 16yrs.

In a recent retrospective review of 55 patients who underwent surgery for tumors of the fourth ventricle over 18 years, it was found that many patients developed neurological and medical complications. This series included both adults and children and various tumor pathologies. Forty-five percent of patients had at least one major neurological complication, while 31% had minor complications. Twenty percent of patients had at least one medical complication. The most common medical complications were respiratory failure (14%), followed by pneumonia (13%)⁷. In this series, the most typical neurological complications were worsening of gait/focal motor disturbance (56%), speech/swallowing deficits (38%), and cranial nerve deficits (31%)⁷. The commonest cranial nerve affected in children with posterior fossa tumors is sixth followed by the seventh nerve. This is called

"floor of the fourth syndrome" which includes an ipsilateral nuclear palsy of cranial nerves VI and VII and contralateral hemiparesis³. In our current series, the incidence of sixth and seventh nerve palsy was 5% each. Even the incidence of lower cranial nerve palsy was only 2.9%. The incidence of cranial nerve palsy in our series was lower as we did not restrict the analysis to only fourth ventricle tumors. In our series, the tumors were both intra and extraventricular. The floor of the fourth ventricle contains many cranial nerve nuclei; hence the incidence of nerve palsy is higher following surgery of fourth ventricle tumors.

Cerebellar mutism is a unique complication of surgery of posterior fossa tumors in children^{8,9,10,11}. A study on two large clinical trials of 450 and 463 medulloblastoma patients, did a prospective survey to evaluate the incidence of Cerebellar mutism syndrome (CMS), its possible causes, and the severity⁸. 24% of the children had CMS of which 43% had severe symptoms, 49% had moderate symptoms and 8% had mild symptoms. Based on both the cohorts, the authors concluded that preoperative brainstem invasion was the only factor that correlated with the CMS. Many patients showed neurocognitive deficits, nonmotor speech/language deficits, and/or ataxia even after one year of diagnosis. Cerebellar mutism was noted in less than 4% of children in our present series.

The non-neurological complications are fever,

Table. 4. Univariate Logistic Regression for Pneumocephalus and Gaze Palsy.

		Pneumocephalus		Gaze palsy	
		OR	P value	OR	P value
Age (years)	<= 3 yr	4.69	0.06	0.63	0.67
Sex	Female	2.27	0.32	0.31	0.28
Shunt done preoperatively	Yes	1.1E+07	0.99	1.71	0.62
Histopathology	Medulloblastoma	1.43	0.75	2.02	0.51
CT Cyst	Yes	1.84	0.49	0.00	0.99
Extension and Spinal seeding	At least one present	3.62	0.15	0.00	0.99
Pre-operative neurological impairment status	Bed bound	0.00	0.99	3.68	0.25
Extent of Resection	Near total resection	1.13	0.88	1.72	0.56
	Subtotal resection	0.00	0.99	7.36	0.04

Table. 5. Univariate Logistic Regression for Lower Cranial Nerve Palsy, Meningitis , and Facial Palsy.

		Lower Cranial Nerve Palsy		Meningitis		Facial Palsy	
		OR	P value	OR	P value	OR	P value
Age (years)	<= 3 yr	0.74	0.78	3.05	0.23	0.88	0.88
Sex	Female	1.70	0.50	3.43	0.18	0.43	0.28
Shunt done preoperatively	Yes	1.2E+07	0.99	0.35	0.26	1.21	0.81
Histopathology	Medulloblastoma	0.36	0.20	1.18	0.91	1.44	0.64
CT Cyst	Yes	1.46	0.66	0.90	0.93	0.31	0.27
Extension and Spinal seeding	At least one present	2.88	0.22	0.00	0.99	0.61	0.64
Pre-operative neurological impairment status	Bed bound	0.00	0.99	6.53	0.11	0.00	0.99
Extent of Resection	Near total resection	1.9E+08	0.99	0.27	0.25	1.74	0.40
	Subtotal resection	1.00	1.00	0.00	0.99	2.30	0.35

Table. 6. Univariate Logistic Regression for Sixth Nerve Palsy, Mutism , and Post-op Hematoma.

		Sixth Nerve Palsy		Mutism		Post-op Hematoma	
		OR	P value	OR	P value	OR	P value
Age (years)	<= 3 yr	0.39	0.37	0.00	0.99	0.00	0.99
Sex	Female	1.63	0.42	0.63	0.56	2.27	0.32
Shunt done preoperatively	Yes	0.71	0.62	0.84	0.83	0.47	0.39
Histopathology	Medulloblastoma	0.84	0.80	0.99	0.99	1.43	0.75
CT Cyst	Yes	1.22	0.78	0.44	0.44	1.84	0.49
Extension and Spinal seeding	At least one present	0.00	0.99	0.85	0.88	3.62	0.15
Pre-operative neurological impairment status	Bed bound	2.30	0.45	0.00	0.99	0.00	0.99
Extent of Resection	Near total resection	2.77	0.15	0.90	0.88	0.56	0.50
	Subtotal resection	3.09	0.23	0.00	0.99	0.00	0.99

pneumocephalus, postoperative pseudomeningoceles, and CSF leaks^{3,12,13,14,15}. The incidence of all these complications together was higher than neurological complications in our series. The syndrome of aseptic meningitis, also called posterior fossa fever, is characterized by spiking fever and meningismus after posterior fossa surgery. Though it is relatively common after surgery for epidermoids or dermoids, it can also be seen following surgical resection of other midline posterior fossa tumors³. Pneumocephalus is not uncommon after fourth ventricular surgery, especially when patients are operated upon in the sitting position. It frequently results from over drainage of CSF through external ventricular drainage during surgery. We do not do surgery in the sitting position; hence, the pneumocephalus incidence was only 2.5% in our series. Postoperative pseudomeningoceles affect 15% to 28% of all children with posterior fossa tumors³. These are self-limited and may respond well to serial lumbar punctures. The CSF leak is a common complication associated with posterior fossa surgery. Leaks usually occur in the early stage of the postoperative period. If the patient has hydrocephalus then a VP shunt is required for treatment of pseudomeningocele and hydrocephalus. The size of the tumor appears to have a positive correlation to the incidence of CSF leakage³. However, we did not find any predictor of postoperative CSF leak.

We analyzed the predictors of complications following surgery for midline posterior fossa tumors. We found that extent of resection was a significant predictor of complications. The odds of complication for near-total resection were 1.94 times more as compared to total resection; the other crucial predictor of complication was the pre-operative shunt. Complications were less for children who had shunt done before surgery. Our logistic regression model's predictive power was only 64%, which means there might have been other predictors of complications unknown or not analyzed by us. We also tried to check the effectiveness of covariates on the type of complications, and none of the variables could significantly predict the specific type of complication in general. When specific complications were analyzed separately, complications like pneumocephalus and gaze palsy had some significant predictive factors like age, extension beyond midline/spinal seeding, and extent of resection. The AUC for these models was better compared to the initial

complication model. Other neurological complications were also analyzed individually, but none could be significantly predicted using any factors considered.

In the series of the fourth ventricular tumor by Ferguson, et al. the surgical approach was found to be a most important predictor of the development of postoperative gait/focal motor deficit, postoperative speech/swallowing deficits, postoperative cranial nerve deficits, and need for postoperative CSF diversion. The telovelar approach was superior to transvermian approach for the preventions of the above complications. The anterior extension predicted the development of postoperative speech/swallowing deficits. The need for postoperative CSF diversion was higher in children⁷. We did not analyze the influence of the surgical approach on the development of complications. As the tumors in our series were intraventricular as well as vermian, the approach to these tumors will be different and cannot be compared. Our preference is telovelar approach for inferiorly placed fourth ventricular tumor, and transvermian for superiorly placed intraventricular tumor.

Limitations

The current study is a retrospective study over many years. Moreover, we did not analyze the impact of the surgical approach or other imaging features to predict complications. The concepts of cerebellar mutism have changed, and the complications following surgery of the midline posterior fossa are no more considered isolated neurological deficits but a spectrum. Henceforth systematic documentation of complications should be done as recommended by the posterior fossa society.

CONCLUSIONS

Complications were not infrequent after surgery for midline posterior fossa in children. The extent of resection and pre-operative shunt were the main determinants of the occurrence of complications. Age below three years and extension beyond midline/spinal seeding were significant predictors of Pneumocephalus. The odds for pneumocephalus were fourteen times more for children below three years and twelve times more for those with extension beyond midline/spinal seeding. Subtotal resection increased the odds for Gaze palsy by nine times compared to total resection. Other Complications could not be significantly predicted in our study. A prospective audit is required and recommended to understand the nature of all

complications and their recovery pattern from midline posterior fossa surgery.

Acknowledgments

My sincere thanks to Dr. Kautilya Patel, junior resident of the Neurosurgery department, for his substantial help during the data collection.

Statement of Ethics

The study complies with the guidelines for human studies and the research was conducted ethically under the World Medical Association Declaration of Helsinki. The subjects (or their parents or guardians) have given their consent and the study protocol was approved by the institute's committee on human research.

Conflict of Interest

The authors have no conflicts of interest to declare.

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