

Fourth Ventricular Epidermoid Cyst – Case Series, Systematic Review and Analysis

Abstract

Background: Epidermoid cysts are extra-axial, pearly white avascular lesions mostly found in the cerebellopontine region. They are slow-growing and mostly become symptomatic when they attain significant size. They do occur at other anatomical locations, but fourth ventricle is a rare location. Three representative cases with their outcomes are described here. **Methods:** The systematic review was done with adherence to predefined criteria. The studied variables were age, gender, duration of symptoms (DOS), clinical features, hydrocephalus (HCP), extent of resection, postoperative complications, outcome, follow-up, and recurrence. Statistical analysis was done to identify predictive factors for outcome. **Results:** Final analysis included 58 studies containing 131 patients. The most common clinical feature was cerebellar dysfunction (93%). The most common cranial nerve involved was the abducens nerve ($n = 37$, 28.46%). Preoperative HCP was present in nearly a third (35%) of patients. The outcomes were not different with age ($P = 0.23$), gender ($P = 0.74$), DOS ($P = 0.09$), and HCP ($P = 0.50$). Improved outcomes were associated with total resections ($P = 0.001$), absence of preoperative cranial nerve dysfunctions ($P = 0.004$), and presentation with features of raised intracranial pressure ($P = 0.005$). Longer DOS (mean 76.74 months) was associated with significantly increased cranial nerve nuclei involvement ($P = 0.03$). Aseptic meningitis was reported in 14.5% of cases. Recurrences were infrequently reported ($n = 9$). **Conclusions:** Although the fourth ventricular epidermoid lesions are difficult to detect in an innocuous stage, when found, they should be extirpated early and totally, as a longer DOS leads to cranial nerve dysfunctions and suboptimal outcomes.

Keywords: Epidermoid cyst, fourth ventricular epidermoid cyst, fourth ventricular tumors

Introduction

Intracranial epidermoid cysts are avascular, pearly white, benign capsulated lesions with inner stratified squamous epithelium, accounting for <2% of all brain tumors.^[1-3] They are thought to be congenital lesions, first described by Cruveilhier, a French pathologist in the early 18th century.^[3-6] They arise as epithelial sequestrations during the 3rd to 5th week of development and persist after neural tube closure.^[7,8] Their growth rate is linear to that of the epidermis.^[9] They become symptomatic, usually in the second to fourth decades of life.^[5,6,10] Tumor grows due to the accumulation of desquamated cells and their breakdown products such as keratin and cholesterol.^[7] Unlike dermoid cyst, they are located off-midline. They are also more common than dermoid cysts.^[7] About half of these intracranial lesions occur in the cerebellopontine angle.^[3,6,11] Epidermoid

cysts are the third most common lesion in this location after vestibular schwannomas and meningiomas.^[5] Other common sites are sellar-suprasellar regions, Sylvian cisterns, basal cisterns, and interhemispheric regions.^[7] Epidermoids in the fourth ventricle occur rarely. Because of its slow-growing nature and tendency to creep in between the neural structures without invading them, they often go unnoticed and become symptomatic only when large.^[9,12] Three of such cases are described here with a literature review and an analysis of data so found.

Case 1

A 36-year-old female presented with mild suboccipital headache and nonpositional vertigo for 5 months. On clinical examination, she had intention tremors involving left upper limb and impaired finger to nose test. She had impaired

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Access this article online

Website: www.asianjns.org

DOI: 10.4103/ajns.AJNS_539_20

Quick Response Code:



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How to cite this article: Kumar S, Sahana D, Rathore L, Sahu RK, Jain A, Borde P, *et al.* Fourth ventricular epidermoid cyst – Case series, systematic review and analysis. Asian J Neurosurg 2021;16:470-82.

Submitted: 12-Nov-2020 **Accepted:** 26-Mar-2021
Published: 14-Sep-2021

tandem gait with a tendency to fall toward left. There were no cranial nerve deficits, and fundus examination was unremarkable. Magnetic resonance imaging (MRI) of the brain showed a multilobulated lesion filling the fourth ventricle's cavity, with an indentation on the brainstem and protruding out through the foramen of Magendie. The lesion was hypointense on T1-weighted image (T1WI) and hyperintense on T2WI, with no contrast enhancement. Diffusion restriction was present in the lesion, suggesting the diagnosis of epidermoid. There was no hydrocephalus (HCP) even though the fourth ventricle was filled with tumor. The patient underwent midline suboccipital craniotomy, and after dural opening, a pearly white tumor wrapped in arachnoid layers was evident at cistern magna. The tumor had displaced the tonsils laterally, filling the fourth ventricle and indenting its floor. After internal decompression, adhered capsular remnants were grasped and dissected away from brainstem using sharp dissection at the brain–tumor interface. Outmost care and patience were taken to avoid injury to critical neural elements on the fourth ventricle floor. The aqueductal opening was visible after tumor removal. The completeness of resection was confirmed with a 30° endoscope. The diagnosis of an epidermoid cyst was confirmed on histology. The patient was discharged on the postoperative day 6 without new neurological deficits. At 43 months of follow-up, there was no recurrence [Figure 1a-c].

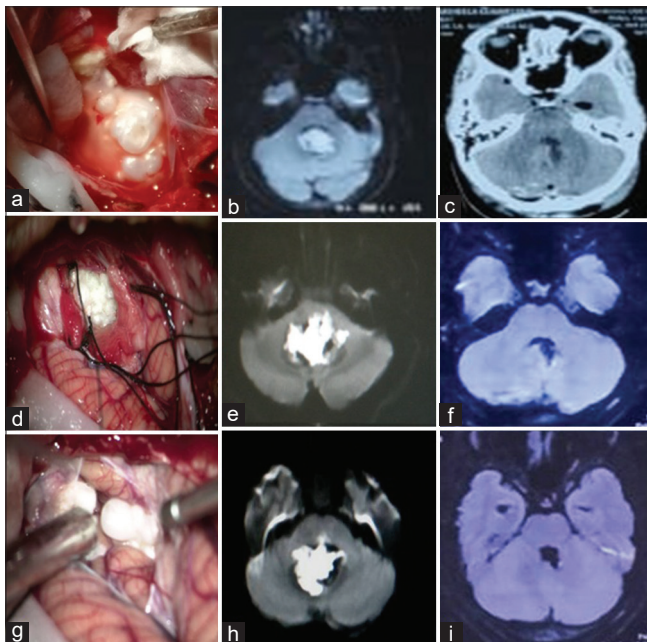


Figure 1: (a-c) Illustrative Case 1 showing pearly white tumor wrapped in arachnoid layers and protruding from the foramen of Magendie along with diffusion restriction and postoperative computed tomography scan, (d-f) Illustrative Case 2 showing avascular capsulated epidermoid filling the cavity of the fourth ventricle with diffusion restriction and postoperative diffusion-weighted imaging, (g-i) Illustrative Case 3 showing epidermoid cyst peeping out through foramen of Magendie with diffusion restriction and postoperative diffusion-weighted imaging

Case-2

A 46-year-old woman had diplopia for 2 years' duration. Diplopia was horizontal and worsened on looking toward left and on looking at distant objects. It resolved on closing the left eye. For this, she was prescribed glasses with a left eye patch. Over the last 6 months, her gait worsened, and she tended to fall toward left. She also had a mild headache. On examination, she had House and Brackmann Grade II facial palsy, left lateral rectus palsy, cerebellar ataxia, and nystagmus along with incoordination of the left side. On imaging, she had a lesion in the fourth ventricle, which was T1 hypointense with some areas of hyperintensity, T2 hyperintense, nonenhancing on contrast, and with diffusion restriction. There was no HCP. She underwent midline suboccipital craniotomy. After separating the tonsils and telovelar dissection, the tumor became visible. Most of the tumor was removed in a piecemeal fashion. The tumor had nubbin insinuating the facial colliculus, it could only be decompressed internally, and a small bit of densely adhered capsule was left behind. The fourth ventricular cavity was inspected with an endoscope. Her preoperative neurological status remained unchanged after surgery. She was discharged on day 8 of surgery. At 26 months of follow-up, her gait had improved, but facial palsy and sixth nerve palsy did not. Repeat MRI did not show any recurrence or areas of diffusion restriction even though a small piece of the capsule could not be removed during surgery [Figure 1d-f].

Case 3

A 26-year-old female presented with a chronic headache of 1-year duration. Headache was intermittent, suboccipital, and increased on coughing without nausea or vomiting. On neurological examination, she had horizontal gaze-evoked nystagmus without any other neurological deficits. Her gait was normal. Computed tomography (CT) scan of the brain showed a hypodense lesion filling the cavity of the fourth ventricle without any HCP. MRI revealed T1 hypointense and T2 hyperintense lesion in the fourth ventricle with diffusion restriction. There was no contrast enhancement. The tumor was approached via midline suboccipital craniotomy. On opening the dura, the pearly white tumor wrapped in arachnoid layers was visible at the foramen of Magendie. We used the facial nerve, lower cranial nerve, and Somato Sensory Evoked Potential monitoring during surgery. The tumor was decompressed internally and dissected from neural structures. Small remnants of the capsule attached to the fourth ventricular floor were dissected carefully using the above-mentioned technique under neuromonitoring and maximum optical magnification, and total excision was achieved. The tumor bed was irrigated with dexamethasone saline. There were no new neural deficits or untoward complications in the postoperative period. She was discharged on day 6 postoperatively. At 8 months of follow-up, there were no recurrence and no new neurological deficits [Figure 1g-i].

Methods

Protocol and registration

This systematic review was done with adherence to Preferred Reporting Items for Systematic Review and Meta-Analysis 2009 criteria throughout the study. The study protocol was predefined to search cases of epidermoid cyst in the fourth ventricle only. This study aimed to gather information and analyze data to manage cases of a fourth ventricular epidermoid cyst. The variable studied were age, gender, duration of symptoms (DOS), presenting symptoms and signs, presence or absence of HCP, extent of resection (EOR), complications, clinical outcomes, recurrence, and follow-up duration. This study being a purely retrospective review of literature, ethical approval was not sought for it. This study was neither funded nor registered with any agency.

Database search

No restrictions were imposed regarding publication date. All review articles, systematic review, meta-analysis, case series, and case reports of fourth ventricular epidermoid were included in the search. This literature review was done in June 2020 with a contribution by all authors. The keywords/MeSH terms searched were -“Epidermoid,” “Fourth ventricle,” “Epidermal cyst,” “Cholesteatoma,” “Keratin cyst,” “Pearly tumor,” “Intraventricular” individually and in combinations. The databases searched were PubMed, Web of Science, Cochrane, Scopus, Medline/Medscape, Ovid, Publons, ScienceDirect, Google Scholar, and Google General Search Engine. The references of selected articles were cross-checked and reviewed to improve the comprehensiveness and included if found eligible. The articles in non-English languages were also screened after Google translation and included if the full text was available. All abstracts and full articles were thoroughly reviewed.

In addition, articles available online, which had vital information, but not included in the indexing agencies, as mentioned above, were also included. Duplication of patients reported in multiple studies was also taken care of and excluded [Figure 2].

Inclusion criteria

1. The studies with human subjects
2. Studies that had substantial information (defined as at least 50% of the ten mentioned study parameters).

Exclusion criteria

1. Studies that do not have substantial information.
2. Cases associated with additional intracranial pathology-confounding factors for outcome
3. Recurrent cases
4. Duplication of patients in other studies.

Data synthesis

In the first step of the literature search, three authors independently searched different databases. Next, two senior authors further reviewed the three sets of selected

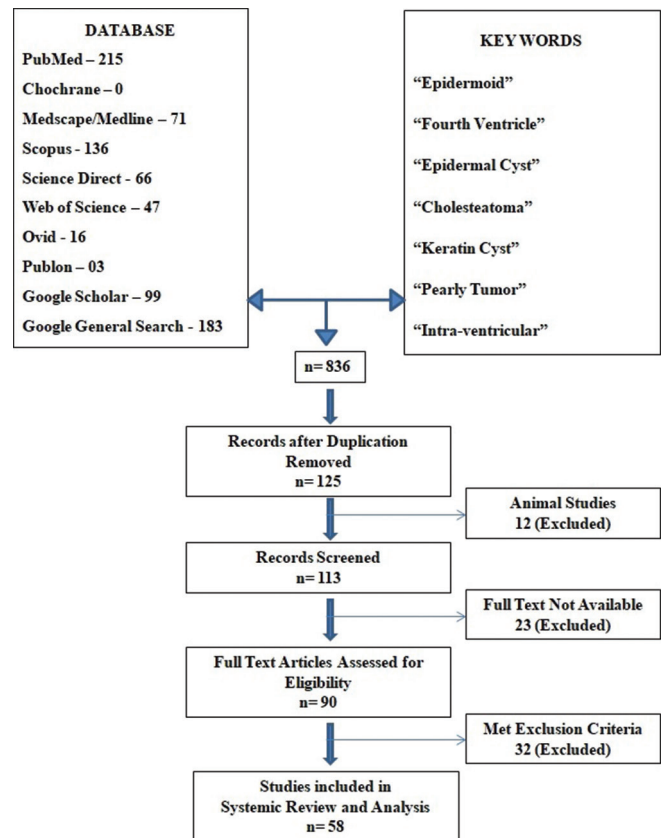


Figure 2: Preferred Reporting Items for Systematic Review and Meta-Analysis Methodology of the systematic review

articles. The articles found common in any of the three sets were included for screening. Two other authors further screened the rest of the articles. The articles thus selected for screening were further reviewed by the senior most authors for their eligibility as per inclusion and exclusion criteria. Disputes regarding the selection of articles were sorted out by voting. For quantitative assessment, clinical parameters were categorized into groups. The description of clinical signs and symptoms had some discrepancies and was categorized based on predefined criteria by authors. Likewise, all complications were categorized for quantitative assessment only. The EOR was labeled as subtotal if any part of the tumor or capsule was left behind. Surgical outcomes were recorded as mentioned in qualified studies and dichotomized between “improved” and “not improved” categories for analysis. Not improved category included death, worsened, and unchanged outcomes.

Statistical analysis

Statistical analysis was done using statistical packages for SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous and categorical variables were evaluated as mean \pm standard deviation (SD). For qualitative analysis, all cases from selected articles were included, but studies with appropriate information were included only for quantitative analysis. Univariate descriptive analysis was done for all variables. Multivariate analysis was

done using the Chi-square test and Fisher's exact test for categorical variables. Continuous variables were analyzed by independent *t*-test and Mann–Whitney U-tests. For multivariate analysis, stepwise logistic regression was applied to analyze the influence of variables on outcome. Two-tailed *P* values were considered statistically significant at $P < 0.05$.

Results

Database search results

A total of 836 studies were found on literature search with an above-described combination of MeSH terms (PubMed – 215, Web of Science – 47, Publons – 3, Medscape/Medline – 71, ScienceDirect – 66, Ovid – 16, Cochrane – 0, Google Scholar – 99, Scopus – 136, Google General Search – 183). Out of these 836 studies, 12 animal studies were excluded. There were 711 duplications of results. In 23 studies, the full text was not available, and 32 studies did not fulfill the inclusion criteria. Eight studies in other languages, which met the inclusion criteria, were included after Google translation.^[13-20] Fifty-eight studies having 131 cases were included in the final review. There was one systematic review,^[21] 13 case series (3 or more cases),^[1,7,9,12,14,15,19,22-27] and 44 case reports (<3 cases) [Table 1 and Figure 2].

Descriptive analysis

Age

Individual data regarding age at presentation was available for 74 patients (50 studies). Case series, which described the mean age of the study population, were excluded from this statistical analysis. The mean age of presentation was 39.80 ± 12.92 years (median 41, range 12–71 years).

Gender

Data about gender were available for 111 patients (55 studies); there were more females ($n = 64$, 57.6%) than males ($n = 47$, 42.4%), with a ratio of 1.36:1.

Duration of symptoms

Data for DOS were available for 89 cases, out of which four case series comprising 30 patients described only their mean value. Thus, mean DOS \pm SD was calculated for 59 patients. The mean DOS was 50.16 ± 87.63 months.

Clinical presentation

Data for clinical signs and symptoms were available for all patients, except one ($n = 130$, total signs and symptoms 336). For analysis, these symptoms were categorized as cerebellar, raised intracranial pressure (ICP), motor, sensory, cranial nerve palsy/paresis (CNP) I, CNP II, CNP III, CNP V, CNP VI, CNP VII, CNP VIII, CNP lower cranial nerves (LCN), and others. Cerebellar signs and symptoms ($n = 121/130$, 93%) were the most common

presentation, followed by cranial nerve involvement. Most commonly involved cranial nerves were VI ($n = 37$, 28.46%), II ($n = 18$, 13.84%), VIII ($n = 17$, 13%), VII ($n = 16$, 12.3%), and LCNs ($n = 12$, 9.2%). Cranial nerves V ($n = 09$), III ($n = 08$), and I ($n = 02$) were infrequently involved. The fourth ventricular epidermoid has a close relationship with the fourth ventricle floor and the underlying cranial nerve nuclei. Therefore, for multivariate analysis, the involvement of cranial nerve I and II was not considered. Features of raised ICP were seen in 74 (56.9%) patients. There were 18 (13.84%) patients with motor impairment, two patients with sensory symptoms, one asymptomatic, and one who had asthma. Individual outcomes could be calculated for 16 patients of motor impairment found in 12 studies, out of which 12 patients (75%) had improved outcomes.

Hydrocephalus

HCP was present in 46 (35.1%) cases of the cohort. As the HCP is an easily noticeable finding on radiological evaluation, for studies that did not mention their absence or presence (59 cases), it was presumed to have been absent. The preoperative ventriculo-peritoneal shunt was placed in 11 cases (23.9%).

Extent of resection

Data for the EOR were available for 121 patients in 52 studies, out of which 63 (52%) patients underwent total resection and 58 (48%) patients underwent subtotal resections. Subtotal resection was defined as leaving behind any trace of tumor or capsule.

Complications

Information about postoperative complications was available in 44 studies (110 patients). Most common complications were aseptic meningitis (AM, $n = 16$, 14.5%), cerebellar ($n = 11$, 10%), CNP VI ($n = 10$, 9%), CNP LCN ($n = 9$, 8.1%), CNP VII ($n = 8$, 7.2%), HCP ($n = 7$, 6.3%), CNP V ($n = 1$), and other nonneurological complications in 15 cases. Out of seven postoperative HCP, six required VP shunt postoperatively.

Outcome

Surgical outcomes were reported in 53 studies, including 125 patients. Ninety-five patients (76%) had improvement in symptoms, while 30 patients (24%) did not improve (unchanged – 18, death – 11, and worsen – 1).

Follow-up

Postoperative follow-up information was reported in 29 studies, including a total of 75 patients. The average follow-up duration was 30 months (range 1–194 months).

Recurrence

Information about recurrences was only reported in nine patients.

Table 1: Literature review of fourth ventricular epidermoid

Author/year/ references	Number	Age	Male/ female	DOS (months)	Described symptoms and signs	HCP (yes/no)	EOR	Complications	Outcome	FU (months)	R
Alpers 1939 ^[1]	1	-	Female	5	Cerebellar; CNP VI; CNP VII; motor	No	-	Other	D	-	-
Pepus <i>et al.</i> , 1968 ^[10]	1	43	Female	18	ICP; CNP II; cerebellar; CNP I; CNP VIII; CNP VI	Yes	ST	Other	D	-	-
Cantu and Ojemann 1968 ^[4]	1	41	Male	-	ICP; cerebellar; CNP III; CNP VI; CNP VIII; CNP V	Yes	ST	AM	I	5	No
Scot 1974 ^[28]	1	38	Female	1.5	Cerebellar; CNP VI; ICP; motor	No	T	Cerebellar	I	194	No
Davis <i>et al.</i> , 1976 ^[29]	1	35	Female	72	CNP VIII; ICP; cerebellar; CNP VI	Yes	T	-	-	-	-
Fawcitt and Isherwood 1976 ^[30]	1	59	Female	-	ICP; CNP II; cerebellar; CNP I	Yes	-	Other	I	36	-
Hanamura <i>et al.</i> , 1978 ^[31]	1	52	Female	72	Cerebellar; CNP VI; CNP VII	Yes	ST	Other	D	-	-
Rosario <i>et al.</i> , 1981 ^[22]	1	42	Male	240	CNP I; cerebellar; ICP; CNP VI; CNP V; CNP VII; motor; sensory	Yes	ST	CNP VII; CNPLCN	W	-	-
Schraeder <i>et al.</i> , 1981 ^[32]	2	46	Male	12	Cerebellar; CNP VII; motor; ICP; CNP V; sensory	No	ST	Other; HCP; CNPLCN	I	24	-
Dubois <i>et al.</i> , 1981 ^[33]	3	30	Male	16	CNP VI; cerebellar; CNPLCN	No	T	CNP I	I	4	-
Gellad <i>et al.</i> , 1982 ^[13]	1	49	Female	84	Cerebellar; CNP VI; motor; CNP III	Yes	ST	HCP ^{II}	I	-	-
Imamura <i>et al.</i> , 1982 ^[34]	1	53	Male	4	ICP; CNP VI; cerebellar; CNP VII	Yes	ST	-	D	-	-
Salazar <i>et al.</i> , 1987 ^[35]	1	35	Male	36	Cerebellar; ICP; CNP VII	No	-	None	I	-	-
Sabin <i>et al.</i> , 1987 ^[23]	2	36	Male	10	ICP; cerebellar	No	-	CNP VI; AM	I	-	-
Bret <i>et al.</i> , 1988 ^[36]	1	45	Female	194	Cerebellar; CNPLCN; CNP VI; CNP II; CNP V; CNP VIII	Yes	ST	Other	UC	5	-
Yuh <i>et al.</i> , 1988 ^[37]	1	44	Female	24	-	Yes ^I	ST	-	I	-	-
Iihara <i>et al.</i> , 1989 ^[38]	1	29	2 male/1 female	12	Cerebellar (2); CNP V (1); CNP III (1); Motor (2); CNP II (2); ICP (1); CNP VIII (1); CNP VII (1)	No	T	-	I	-	No
Bret <i>et al.</i> , 1988 ^[36]	2	41	female	48	Cerebellar (2); CNP V (1); CNP III (1); Motor (2); CNP II (2); ICP (1); CNP VIII (1); CNP VII (1)	Yes	T	-	I	-	No
Yuh <i>et al.</i> , 1988 ^[37]	3	43	female	168	Cerebellar (2); CNP V (1); CNP III (1); Motor (2); CNP II (2); ICP (1); CNP VIII (1); CNP VII (1)	Yes	T	-	UC	-	No
Bret <i>et al.</i> , 1988 ^[36]	1	52	Male	12	ICP; cerebellar	Yes	T	AM	I	24	-
Yuh <i>et al.</i> , 1988 ^[37]	1	28	Female	-	Cerebellar; CNP VII	No	T	-	I	-	-
Iihara <i>et al.</i> , 1989 ^[38]	2	35	Female	144	ICP; CNP II; cerebellar	Yes ^I	-	-	I	-	-
Iihara <i>et al.</i> , 1989 ^[38]	1	32	Male	144	CNP VI; CNP VII; cerebellar; motor	No	ST	AM	UC	1	-

Contd...

Table 1: Contd...

Author/year/ references	Number	Age	Male/ female	DOS (months)	Described symptoms and signs	HCP (yes/no)	EOR	Complications	Outcome	FU (months)	R
Yamakawa <i>et al.</i> , 1989 ^[39]	1	19	Female	12	Cerebellar (2); ICP (1); CNP VI (2); CNP VIII (1); CNP II (1); CNP III (2)	No	ST	None	I	-	No
	2	46	Female	60		No	ST	None	I	-	No
Sakamoto <i>et al.</i> , 1989 ^[40]	1	41	Male	60	ICP; others (asthma); cerebellar; CNP II	No	T	None	I	2	-
Lunardi <i>et al.</i> , 1990 ^[24]	7	40*	3 male/4 female	24*	Cerebellar (7); CNP VI (7); CNP V (2)	No	T 1	AM (3); none (4)	D (2)	72*	Yes (1)
							ST 6		UC (5)		
Isla <i>et al.</i> , 1990 ^[14]	4	35*	2 male/2 female	48*	ICP (4); cerebellar (4); CN II (2) CNP V (1); CNP III (2); CNPLCN (1)	Yes (4)	T 3	-	I (2)	64*	-
							ST 1		UC (2)		
Wagle <i>et al.</i> , 1991 ^[41]	1	60	Male	180	Cerebellar; ICP; CNP VI	Yes	-	-	-	-	-
	2	44	Female	-	Cerebellar; CNP VI	No	-	-	-	-	-
Bini <i>et al.</i> , 1993 ^[7]	1	46	Female	0.75	Cerebellar	No	T	CNP VI	I	3*	-
	2	57	Female	36	Cerebellar	No	T	Other; CNP VII; motor; CNP V	I		-
Misra <i>et al.</i> , 1994 ^[42]	3	34	Male	-	Cerebellar; CNP III	No	T	Cerebellar; CNP VI	I		-
	1	66	Male	564	Cerebellar; CNP VI; motor	No	T	-	I	15	No
Nassar <i>et al.</i> , 1995 ^[9]	1	53	Male	6	Cerebellar; ICP; CNP II	No	T	AM; HCP ^{II}	I	-	-
	2	25	Male	1	Cerebellar; CNP II	Yes ^I	T	Other	I	156	-
	3	31	Female	24	Cerebellar; ICP	No	ST	CNP VII; cerebellar	I	24	-
	4	49	Female	1.5	Cerebellar; ICP	Yes	T	Cerebellar; CNP VI; Other	I	6	-
Taguchi <i>et al.</i> , 1997 ^[15]	1	48	Female	120	Cerebellar	No	T	Other	I	60	No
	2	29	Female	2	Cerebellar; CNP VI	No	T	None	I	14	No
	3	62	Female	3	Cerebellar; CNPLCN; motor	No	ST	None	UC	12	No
	4	37	Female	22	Cerebellar; CNP V; CNP VII; CNPLCN	No	ST	Other	I	31	No
Talacchi <i>et al.</i> , 1998 ^[25]	5	54	Female	72	Cerebellar; CNPLCN	No	ST	Other	I	18	No
	5	-	-	-	ICP (3); cerebellar (5); CNP VI (2); CNP VIII (1); CNPLCN (2); CNP VII (1); Motor (1); CNP II (1)	Yes (4) No (1)	T-3 ST 2	None (5)	D (1) I (2) UC (2)	-	-
Tancredi <i>et al.</i> , 2003 ^[1]	9	46.2*	6 male; 3 female	26*	Cerebellar (8); ICP (4)	Yes (3)	ST 7	AM (1); HCP ^{II} (1)	I (7)	174*	Yes (3)
Kambe <i>et al.</i> , 2003 ^[2]	1	26	Male	36	ICP; cerebellar; CNP VIII	No (6)	T 2	None (8)	D (2)	-	-
						No	T	None	I	-	-
Jeon <i>et al.</i> , 2005 ^[43]	1	43	Female	12	ICP; cerebellar	Yes	T	None	I	4	No

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Author/year/ references	Number	Age	Male/ female	DOS (months)	Described symptoms and signs	HCP (yes/no)	EOR	Complications	Outcome	FU (months)	R
Cekic <i>et al.</i> , 2005 ^[44]	1	19	Female	-	ICP; cerebellar	No	T	-	-	-	-
Hila <i>et al.</i> , 2006 ^[16]	1	24	Male	0.5	ICP; CNP II; cerebellar	Yes	T	None	I	5	-
Meng <i>et al.</i> , 2006 ^[26]	8	32-56	5 male/3 female	-	ICP (6); cerebellar (3); motor (2); CNP VIII (8)	Yes (3) No (5)	T 5 ST 3	AM (2); none (6)	I (8)	47*	Yes (1)
Forghani <i>et al.</i> , 2007 ^[5]	1	28	Female	24	Cerebellar	No	ST	None	I	-	-
Trijolet <i>et al.</i> , 2008 ^[17]	1	30	Female	12	ICP; CNP VIII; cerebellar	No	-	-	I	-	-
Lauvin <i>et al.</i> , 2009 ^[45]	1	30	Female	12	ICP; cerebellar	No	T	-	-	-	-
Agrawal <i>et al.</i> , 2009 ^[46]	1	26	Male	-	Other (asymptomatic)	No	T	None	I	-	-
Aggouri <i>et al.</i> , 2010 ^[18]	1	44	Female	2	ICP; cerebellar	No	ST	None	I	18	No
Moumen <i>et al.</i> , 2010 ^[19]	1	45	Male	12	ICP; CNP II; cerebellar	Yes	T	None	I	9	-
	2	58	Male	36	ICP; cerebellar	No	ST	None	I	12	-
	3	39	Female	48	ICP; cerebellar; CNP II; CNP VI	Yes ⁱ	ST	None	I	33	-
Su and Young 2011 ^[47]	4	49	Female	96	Cerebellar; ICP; motor	Yes ⁱ	T	Other	I	48	-
	1	37	Female	-	Cerebellar; ICP	No	-	-	I	-	No
Bohara <i>et al.</i> , 2011 ^[8]	1	12	Male	-	CNP VI	No	T	-	I	-	-
Oulali <i>et al.</i> , 2012 ^[20]	1	64	-	18	Cerebellar; ICP	Yes	ST	None	I	12	-
Mathai <i>et al.</i> , 2013 ^[48]	1	45	Female	6	Cerebellar; ICP	No	ST	AM	I	3	-
Chowdhury <i>et al.</i> , 2013 ^[49]	1	19	Male	-	Cerebellar; ICP; motor	No	T	None	I	-	No
	2	71	Male	-	ICP; CNP II; cerebellar	No	-	None	I	-	-
Raghunath <i>et al.</i> , 2013 ^[27]	10	43.1*	5 male/5 female	10*	Cerebellar (8); ICP (4); CNP VII (2)	Yes (2) ⁱ	T 3 ST 7	CNP VII (2); CNPLCN (2); cerebellar (1); HCP ⁱⁱ (1); None (4)	D (2) UC (3) I (5)	17.2	No
Sengupta and Singh 2015 ^[50]	1	54	Male	0.5	Cerebellar	No	T	-	I	6	-
Gopalkrishnan <i>et al.</i> , 2014 ^[12]	13	38*	-	-	Cerebellar (9); CNP VIII (1); ICP (9); CNPLCN (3); CNP VII (3); CNP VI (4); Motor (2)	No	T 9 ST 4	CNP VI (3); CNP VII (2); CNPLCN (2); cerebellar (5); HCP (1) ⁱⁱ	I (13)	-	Yes (4)

Contd...

Table 1: Contd...

Author/year/ references	Number	Age	Male/ female	DOS (months)	Described symptoms and signs	HCP (yes/no)	EOR	Complications	Outcome	FU (months)	R
Tuchman <i>et al.</i> , 2014 ^[51]	1	50	Female	-	Cerebellar	No	ST	AM	UC	-	-
Taschner <i>et al.</i> , 2015 ^[52]	2	24	Female	-	ICP; CNP VI	No	T	AM	UC	-	-
	1	39	Female	2	Cerebellar; ICP	No	ST	CNPLCN	I	-	-
Patil <i>et al.</i> , 2016 ^[53]	1	27	Male	7	Cerebellar	Yes	ST	-	-	-	-
Akchakaya <i>et al.</i> , 2016 ^[54]	1	51	Female	36	ICP; cerebellar	No	T	None	I	-	-
Cardoso <i>et al.</i> , 2016 ^[3]	1	48	Female	6	ICP; cerebellar	Yes ¹	T	None	I	6	-
Kokkalis <i>et al.</i> , 2018 ^[55]	1	16	Female	96	ICP; cerebellar	Yes	T	None	I	24	No
Chung <i>et al.</i> , 2017 ^[21]	1	21	Female	3	ICP; CNP II; CNP VI	Yes	T	CNP VII; CNP VI	I	1	No
Veretennikov <i>et al.</i> , 2018 ^[56]	1	49	Female	9	CNP VI; CNP VII; CNP VIII	No	ST	Other	I	10	-
Bryl <i>et al.</i> , 2018 ^[6]	1	37	Female	-	Cerebellar; CNP VI; Motor	No	T	Cerebellar; CNPLCN; CNP VI	I	7	No
Kaba <i>et al.</i> , 2019 ^[57]	2	27	Female	-	ICP	No	T	AM; other	I	1	No
	1	21	Female	-	ICP; cerebellar; CNP II	Yes ¹	ST	None	I	12	No
	2	33	Female	3	Cerebellar; CNP II	Yes ¹	ST	AM; HCP ¹¹	I	7	No
Kumar <i>et al.</i> , 2019 ^[58]	1	30	Female	1.5	ICP; cerebellar; CNP II	Yes ¹	T	None	I	67	No

Cases described by Mouden *et al.*, 2010^[9] were re published by Hossini *et al.*, in 2012^[59] and Saqui *et al.*, 2017^[60] Cases reported by Tancredi *et al.*, 2003^[11] includes published by Fiume *et al.*, 1998 (7 cases)^[61] excluded from analysis. Other complications - (unconscious; bradycardia; fever; atetosis; personality change; non neurological; vomiting; collapsed on table; excessive bleeding; chronic; SDH; pneumocephalus; executive dysfunction; low GCS; bacterial meningitis; CSF leak). Other signs and symptoms includes - asthma; asymptomatic. *Study mean; Preoperative VP shunt; Postoperative VP shunt. AM -Aseptic meningitis; DOS - Duration of symptoms; FU - Follow-up; R - Recurrence; HCP - Hydrocephalus; ICP - Intracranial pressure; EOR - Extant of resection; T - Total resection; ST - Subtotal resection; CNP - Cranial nerve palsy; CNP I - Olfactory nerve; CNP II - Optic nerve; CNP III - Oculomotor nerve; CNP V - Trigeminal nerve; CNP VI - Abducens nerve; CNP VII - Facial nerve; CNP VIII - Vestibulocochlear nerve; LCN - Lower cranial nerve; D - Dead; W - Worsened; I - Improved; UC - Unchanged; CSF - Cerebrospinal fluid; GCS - Glasgow Coma Scale; SDH - subdural hematoma; VP - Ventriculoperitoneal

Table 2: Cross tabulation and statistical analysis of studied variables									
Variables	Gender (male/female)		ICP (yes/no)		CNP (yes/no)		HCP (yes/no)		EOR (total/ST)
ICP (yes/no)	50 studies, 81 cases								
	Male	Female	P						
	Yes	18	28	0.65 (NS)					
	No	12	23						
CNP (yes/no)	51 studies, 94 cases		53 studies, 95 cases						
	Male	Female	P						
	Yes	20	27	0.83 (NS)	Yes	23	24	0.08 (NS)	
	No	19	28		No	32	16		
HCP (yes/no)	52 studies, 92 cases		39 studies, 57 cases		53 studies, 95 cases				
	Male	Female	P						
	Yes	13	20	0.84 (NS)	Yes	25	6	0.001 (S)	Yes 14 19 0.31 (NS)
	No	22	37		No	9	17		No 33 29
EOR (total/ST)	44 studies, 64 cases		46 studies, 75 cases		46 studies, 85 cases		48 studies, 89 cases		
	Male	Female	P						
	T	16	21	0.15 (NS)	T	25	16	0.14 (NS)	T 18 24 0.23 (NS)
	ST	7	20		ST	15	19		ST 24 19
Outcome (I/NI)	46 studies, 80 cases		48 studies, 97 cases		47 studies, 89 cases		50 studies, 101 cases		44 studies, 89 cases
	Male	Female	P						Total Subtotal P
	I	25	38	0.74 (NS)	I	52	26	0.005 (S)	I 29 41 0.004 (S)
	NI	6	11		NI	6	13		NI 15 04

ICP - Intra cranial pressure sign/symptoms; CNP - Hydrocephalus; EOR - Extant of resection; T - Total resection; ST - Subtotal resection; I - Improved; NI - Not improved; NS - Not significant; S - Significant

Multivariate analysis

Age

The mean age was not significantly different among males and females (70 patients, 48 studies). Mean age of presentation of males ($n = 25$) was 40.32 ± 15.29 years and for females ($n = 45$) was 39.11 ± 11.50 years ($P = 0.87$). There was a weak positive correlation between age and DOS (41 studies, $n = 55$, Pearson r value = 0.029, $P = 0.025$). Statistical significance was also not found between age and raised ICP (47 studies, 68 patients, $P = 0.804$), age and CNP (48 studies, 70 patients, $P = 0.485$), age and HCP (50 studies, 74 patients, $P = 0.53$), and age and outcomes (45 studies, 68 patients, $P = 0.21$). Age and EOR were analyzed for 65 patients from 45 studies. On the independent t -test, the mean age of patients who underwent subtotal resection (42.60 ± 11.30 years, standard error of the mean [SEM] = 2.13 years) was significantly higher ($P = 0.04$) than those who underwent total resection (36.351 ± 13.05 years, SEM = 2.14 years).

Gender

Analysis between gender and other variables did not reach statistical significance (gender with DOS – 41 studies, 55 patients, $P = 0.164$; gender with ICP – 50 studies, 81 patients, $P = 0.655$; gender with CNP – 51 studies, 94 patients, $P = 0.83$; gender with HCP – 52 studies, 92 patients, $P = 0.84$; gender with EOR – 44 studies, 64 patients, $P = 0.15$; gender with the outcome – 46 studies, 80 patients, $P = 0.74$).

Duration of symptoms

When DOS was analyzed concerning other variables, the only variable where statistical significance was present was with CNP (40 studies, 55 patients). Patients with CNP have significantly ($P = 0.03$) longer DOS (mean 76.740 ± 121.1 months) than patients who do not have CNP (mean 26.29 ± 38.35 months). Although the mean DOS with features of raised ICP was 38.06 ± 55.89 months in comparison to 68.96 ± 128.95 months without features of raised ICP, but this difference did not reach significance (39 studies, 53 patients, $P = 0.233$). There was no statistical significance in DOS with HCP (42 studies, 59 cases, $P = 0.53$). DOS was lesser in the improved group than the improved group (38 studies, 55 patients, mean DOS 40.01 months vs. 94.22 months); however, this difference did not reach statistical significance ($P = 0.09$).

Cranial nerve dysfunction

Multivariate analysis showed that preoperative cranial nerve dysfunction is significantly ($P = 0.004$) related to outcomes “not improved.” This significance was also confirmed on logistic regression (47 studies, 89 patients, $P = 0.006$). However, there was no significant difference with HCP (53 studies, 95 cases, $P = 0.31$) and with

EOR (46 studies, 85 patients, $P = 0.23$). Likewise, the incidence of CNP was not significantly higher with features of raised ICP (53 studies, 95 patients, $P = 0.08$).

Hydrocephalus

Correlation of HCP with outcomes or with other variables did not reach statistical significance (HCP with EOR – 48 studies, 89 cases, $P = 0.85$ and HCP with the outcome – 50 studies, 101 patients, $P = 0.50$).

Outcome

The outcomes were significantly different among EOR, as total resection was better than subtotal resections (44 studies, including 89 patients, $P = 0.001$, logistic regression, $P = 0.002$). However, EOR did not significantly affect postoperative neurological complications, including AM (35 studies, 57 patients, $P = 0.81$). Outcomes were significantly better in patients presenting with raised ICP (48 studies, 97 patients, $P = 0.005$). Cross tabulation and statistical analysis of variables have been summarized in Table 2.

Overall, the outcomes were affected by three variables – ICP, CNP, and EOR. When these factors were analyzed together in stepwise logistic regression, all were significant ($P = 0.01$, 0.01, and 0.03).

Discussion

As the fourth ventricle is a rare location for epidermoid cysts, randomized trials for this entity are far from possible, and all conclusions need to be drawn out of the information obtained from case series and case reports. There was only one available systematic review that analyzed the outcomes and the clinical variables. Chung *et al.* included only 23 studies and 37 patients and excluded certain cases with substantial information.^[21] Our analysis included 58 studies, including 131 patients, which was much higher than the mentioned study. Chung *et al.* found longer age and DOS as predictors of outcome.^[21] In our study, increasing age has significantly higher chances of subtotal resections, probably due to chronic presence, leading to adherences to neurological structures. The mean age, however, did not significantly affect the outcomes. Likewise, longer DOS significantly increased the chances of cranial nerve dysfunctions but did not affect outcomes. It is noticeable that the mean age of presentation and DOS are similar in both the reviews. Similarly, there were more females than males in both reviews.

The results of our study have few sharp contrasts compared to the study by Chung *et al.* In our study, 93% of patients had cerebellar signs and symptoms in comparison to 67.6% of patients in the study by Chung *et al.* Similarly, the percentage of cranial nerve dysfunctions and HCP was more in our study.^[21] This difference is probably due to the inclusion of a higher number of patients for analysis in our study. Although fourth ventricular epidermoids fill up

the fourth ventricle, HCP always does not occur. HCP was present in about one-third (35%) of patients in this cohort. It was postulated that cerebrospinal fluid seeps between the interstices of the tumor's capsule and maintains the outflow.^[1,5,9,22,49] Some authors had reported remission of symptoms once the tumor extrudes through the foramen of the fourth ventricle.^[9,24]

This analysis explored possible associations between multiple variables and their effects on outcomes. The only predictors affecting outcomes were presence of features of raised ICP, preoperative cranial nerve dysfunctions, and the EOR. As decompression of these lesions restores the CSF flow, symptoms of raised ICP are almost immediately relieved. Presence of cranial nerve palsy often suggests brainstem involvement and heralds poor outcome. Epidermoids, being extra-axial and avascular lesions, are generally considered easy to remove surgically, but this is not always so in cases of fourth ventricular epidermoids.^[24,48] Adherence of the capsule to vital neurological structures, especially with brainstem and its nuclei, often leads to subtotal resections.^[1,12,21,24,25] Many surgeons prefer subtotal resection in such cases, but this analysis emphasizes the role of total resections. Authors do not debate the importance of patient safety during surgery, but total removal is often possible under neuromonitoring in selected cases with meticulous dissection. Careful dissection of the capsule from arachnoid layers is the surgical pearl for removing this pearly tumor.^[26] Endoscopic assistance may help visualize tumors in otherwise inaccessible areas.^[51] The risks associated with total resection attempts should not outweigh the benefits, and subtotal removal may be justified in some cases.^[9,25,27] We analyzed the risks of postoperative neurological and tumor-specific complications such as AM and found that total resections were not associated with higher complications, contrary to popular belief. During the internal decompression, every effort to avoid spillage of the tumor needs consideration. Spillage and incomplete removal may cause AM requiring steroids.^[4,35] However, in this review, only 16 patients (14.5%) had AM.^[1,4,6,9,13,24,26,36,38,48,51,57]

Incomplete resection may lead to late recurrences requiring surgery.^[1] As previously mentioned, there is scarce reporting of recurrences; only nine cases were reported in the literature at a mean follow-up period of 30 months.^[1,12,24,26] Scott *et al.* mentioned the most prolonged duration of follow-up (194 months), and after total resection, there was no recurrence; however, after a mean follow-up duration of 174 months, Tancredi *et al.* observed three recurrences in seven subtotal resections.^[1,28] In one of our patients, where a tiny piece of capsule adherent to the brainstem was left behind, 26 months of follow-up did not show recurrence on MRI. However, we agree that with this short follow-up duration for such a slow-growing tumor, it is not prudent to conclude the incidence of recurrence.

Before advancements in technology, neurosurgeons did not have the luxury of imaging tools available today. In the pre-CT era, most cases were diagnosed on plain X-ray, pneumo-encephalogram, ventriculogram, and arteriogram.^[13,36] Evolution of imaging modalities has led to early detection of these lesions and prompt reporting. On CT, epidermoids appear as nonenhancing hypodense lesions with mass effect.^[29] CT may show calcification at times.^[30] MRI has now become the diagnostic modality of choice.^[5,6,8] Epidermoids are hypointense on T1WI and heterogeneously hyperintense on T2WI. When protein and triglyceride contents of tumors are high, they appear hyperintense on T1WI and are known as “white epidermoids.”^[5,53] These lesions are well encapsulated and insinuate into cisterns. Due to their slow-growing nature, they deform the surrounding structures, and despite significant compression, perilesional edema is absent. They do not enhance with gadolinium and show diffusion restriction.^[37] In the fourth ventricle, they produce signals similar to CSF on T2WI and can be differentiated by the absence of suppression on FLAIR images.^[5,44] Pathological slides show a nuclear attenuated squamous epithelium without atypia. Unlike in dermoid cyst, dermal inclusion structures are absent. Malignant changes are rare.^[5,33]

Limitations

The study, being retrospective in nature, has certain limitations. Some studies published in radiological journals got excluded as they did not qualify the inclusion criteria due to limited clinical information. Factors such as age, DOS, and follow-up durations were described as mean in some case series and get excluded from the final statistical analysis. Data for DOS were missing in many studies. Clinical signs and symptoms have been described vaguely in different studies, thus needed categorization for the statistical analysis.

. Further, certain symptoms may be attributed to more than one neurological structure and were categorized based on the authors' opinion, which may vary. One such example is “nystagmus and ataxia;” both may be attributed to either cerebellar or vestibular dysfunction or both. The information about the presence or absence of HCP was incomplete in many studies. As HCP is hard to miss finding on imaging, authors presumed their absence in cases where this description was absent. Likewise, the EOR was described in various studies as total or gross total resection even when “some part of the capsule” was left behind. In our analysis, any part of the tumor or capsule left behind was considered as subtotal resection. Postoperative complications, follow-up duration, and recurrences were scarcely mentioned in studies.

Conclusions

The fourth ventricle epidermoid is a relatively rare entity. Determining its incidence is, therefore, difficult

at this stage. Our study determined that total resection and preoperative absence of cranial nerve involvement predicted better postoperative outcomes in such patients. In addition, a longer DOS was associated with higher chances of cranial nerve nuclei involvement. Early detection of this innocuously slow-growing tumor may not be feasible but, when found, needs adequate surgical resection to help improve outcomes.

Acknowledgments

Authors would like to thank Dr. Shashank Nahar and Dr. Naman Chandrakar (MCh students), Department of Neurosurgery, DKS Post Graduate Institute and Research Center, for their helpful suggestions and motivations during the writing of this manuscript. The suggestions and statistical analysis by Dr. Kittu Jain were invaluable to the completion of this review. Authors are also thankful to Dr. Hemant Sharma, Assistant Superintendent, for providing optimal library access for literature search and statistical analysis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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