



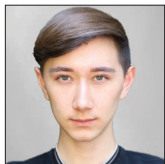
Review Article

Predictors for complete surgical resection of posterior fossa neurenteric cysts: A case report and meta-analysis

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Received : 22 July 2021

Accepted : 16 September 2021

Published : 19 October 2021

DOI

10.25259/SNI_723_2021

Quick Response Code:



ABSTRACT

Background: Incomplete resection of neurenteric cysts (NCs) has been associated with increased recurrence rates in patients compared to complete resection (CR) and information on intracranial NCs appearance on diagnostic imaging is scarce. We sought to identify factors associated with CR and provide the largest up-to-date review of NCs appearances on various diagnostic images.

Methods: Data from Medline, EMBASE, and Web of Science were extracted. Univariate and multivariate logistic regression models were used to analyze factors associated with CR.

Results: A total of 120 publications reporting 162 original cases on posterior fossa NCs met the inclusion criteria for analysis. Eighty-nine (55.6%) of the patients were female, the mean (SD) age of the patients' during operation was 34.3 (16.9) years, and CR was achieved in 98 (60%) of patients. Univariate analysis identified male sex as a statistically significant predictor for complete resection (OR 2.13, 95% CI 1.10–4.11, $P = 0.02$). The retrosigmoid approach (OR 1.89, 95% CI 0.98–3.63, $P = 0.06$), far lateral approach (OR 0.46, 95% CI 0.21–1.02, $P = 0.06$), and pediatric patient (OR 2.45, 95% CI 0.94–6.56, $P = 0.07$) may be possible predictors for CR, however, they were not statistically significant. NCs are mainly hypodense on CT (32 [61.5%]), varied greatly in intensity on T1WI, hyperintense on T2WI magnetic resonance imaging (98 [67.1%]), and hyperintense on fluid-attenuated inversion recovery (17 [63.0%]).

Conclusion: We recommend utilizing various diagnostic imaging tests to help reduce misdiagnoses when identifying intracranial NCs. For patient safety, CR should be achieved when possible, to reduce risk of additional operations due to recurrence.

Keywords: Magnetic resonance imaging, Neurenteric cyst, Posterior fossa tumor, Resection

INTRODUCTION

Neurenteric cysts (NCs) are extremely rare, benign, congenital endodermal lesions originating from the central nervous system. At present, the exact etiology of NCs is unknown.^[20,24] However, the main theory suggests that during the 3rd week of embryological development, it is a result of the failure of the notochord to separate from the foregut during the process of exhalation. This is said to result in the endodermal cells to be incorporated into the notochord and ultimately

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contributing to the cyst's formation. The most common location for NCs are found to occur along the spinal cord than intracranially.^[8] Out of the reported intracranial NCs, 72.2–90% are located in the posterior fossa while typically occurring at the midline and extending along the medulla and pons.^[24] Symptoms reported vary depending on the location and size of the cyst, however, they are most often reported to carry an insidious onset.^[9] Therefore, the intracranial cyst has been able to remain asymptomatic and undetectable until the third and fourth decades of life. When symptoms are noticeable, the induced intracranial pressure has reported to cause headaches, nausea, seizures, and motor defects depending on structures under compression.^[1] On magnetic resonance imaging (MRI), the cysts are known to have various appearances in signal intensity. Therefore, the final diagnosis of NCs is established on histopathology after its resection. MRI is the method of choice to define the lesion preoperatively,^[20] and surgical removal is currently the only effective treatment.^[5] Subtotal or incomplete resection (IR) of the cyst has shown to be associated with increased recurrence rates for patient^[5,6,10,12,14] and a long-term follow-up over many years is necessary as delayed recurrences may occur.^[18] The purpose of our study is to analyze various preoperative factors which may affect resection outcome along with providing the most up-to-date review on the cyst's appearance on diagnostic images. The preoperative factors identified with having an association with the resection outcome could help surgeons to better understand the status of their patient in terms of risks before the patient undergoing surgery.

CASE REPORT

We present a case of a 36-year-old male who was admitted to the hospital due to a 1-month history of daily headaches within the occipital region. The headaches were reported to be worse at night and occasionally accompanied by nausea and dizziness. Neurological examinations revealed a right-sided exaggerated tendon reflex compared to the contralateral side. The patient was diagnosed with a positive pyramidal syndrome, Hoffmann's reflex, and Babinski's and Rossolimo's sign on the right side. A CT scan revealed a $20 \times 15 \times 23$ mm isodense focal lesion in the posterior fossa at the level of the foramen magnum [Figure 1a]. The lesion extended to the level of the dens of axis while compressing the spinal cord posteriorly. Proton density [Figure 1b], T1 [Figure 1c and d], and T2 [Figure 1e and f] weighted MRI scans revealed a $22 \times 11 \times 33$ mm well-defined cystic mass with two heterogeneous compartments within the foramen magnum at the level of C1-2. The medulla and spinal cord were shown to be displaced and compressed along with remodeling of the vertebral arteries with the right artery mainly affected. The superior half of the lesion was hyperintense on T2WI [Figure 1e] and moderately hypointense on T1WI MRI [Figure 1c]. The inferior half of the lesion was hypointense on T2WI and hyperintense on T1WI MRI. No enhancement was shown after contrast administration. After careful consideration, the far lateral approach was chosen, and the patient underwent preparation for the procedure. A J-shaped skin incision followed by a suboccipital craniotomy, C1 laminectomy, and

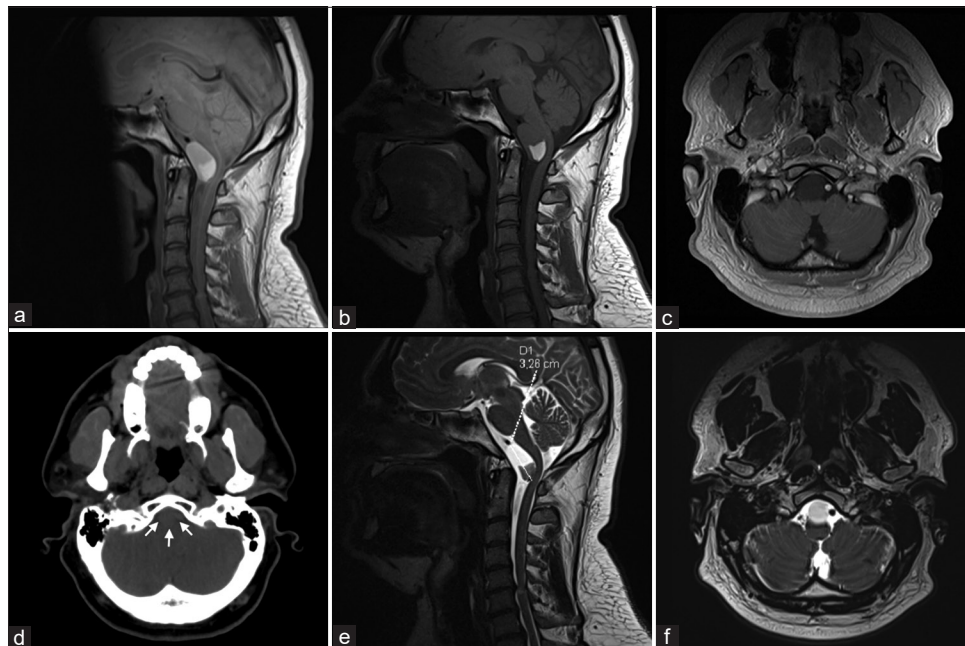


Figure 1: Preoperative scans reveal a lesion located at the ventral craniocervical junction. The lesion is shown hyperintense on PD-weighted imaging (a, sagittal), heterogeneous on T1-weighted (b, sagittal; c, axial), isodense on CT (d, axial), and hyperintense on T2-weighted MRI (e, sagittal; f, axial).

a C2 hemilaminectomy was performed. The dura was opened, exposing the extramedullary cyst. Complete resection (CR) was achieved and a cranioplasty with a typical closure concluded the operation. A histological examination revealed the cyst to be most consistent with a type B NC. The postoperative course was uneventful, and the patient was discharged on the 7th day without any neurological deficits. In a later follow-up, a CT scan revealed no sign of cyst recurrence.

METHODS

Search strategy

The screening process was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The databases of Medline, Web of Science, and EMBASE were used to retrieve studies from inception to March 14, 2021, without language limits. The following keywords were used in all three databases: (“cyst”/exp OR cyst AND (neurenteric OR endodermal OR enterogenous OR enterogenous OR epithelial OR teratomatous OR enterogenic OR “foregut”/exp OR foregut OR respiratory OR bronchogenic) OR intestinoma OR gastrocytoma AND (foramen OR magnum OR craniocervical OR craniovertebral OR craniospinal OR posterior AND fossa OR cerebellopontine)).

Selection criteria

The search was performed independently by three authors (SA, PB, and SP) and two additional authors (TS and JF) arbitrated any disagreements on inclusion or exclusion of the studies. All case reports related to NCs located specifically in the posterior fossa were evaluated. Studies that did not report the extent of the surgical resection of the cyst (complete or incomplete) were excluded from the study. The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports was used to evaluate the quality of the reports. We considered the studies that included at least four of the eight criteria suitable to be used in our study.

Data extraction

The results of the surgical resection reported by the studies were classified into two groups: CR and IR. CR was only recorded if stated in the report. All other reported results such as near-total, subtotal, or partial resections were recorded as IR. The data from the first operation on a patient were included in our study. Therefore, any additional operations undergone by a patient due to cyst recurrence were excluded from the study. Readings from diagnostic images from the case reports collected were categorized into one of three groups by their intensity (H, hyperintense; G, isointense; and B, hypointense). Patient sex, age, cyst location, surgical approach, and NC type were also extracted.

Statistical methods

Comparison of CR and IR was conducted using Chi-square or Fisher’s exact test for categorical variables. For continuous variables, Student’s t-test or Mann–Whitney U-test was used. To find the potential factors associated with CR, a univariate binary logistic regression model was used. For diagnostic images, data reporting either isointense (G) from MRI or isodense (G) from CT were excluded to dichotomize the variables. All variables with $P < 0.25$ from the univariate analysis were then used in a multivariate binary logistic regression model to calculate multivariate-derived odds ratios. $P < 0.05$ was considered statistically significant. Statistical analysis was conducted using IBM SPSS Statistics version 26 (IBM Corp.).

RESULTS

Search strategy

A total of 822 references were identified by the three databases, as shown in [Figure 2]. After the removal of duplicates, 475 references remained and underwent the first screening process. The title and abstract were analyzed, and 270 references were removed as they did not pertain to NCs. The remaining 205 references underwent a full-text evaluation. The references had pertained to NCs located in the posterior fossa including the extent of the surgical resection. Forty-nine references were removed as they did not pertain to NCs in the posterior fossa. Twenty-six references failed to mention the extent of the resection, six references reported no operation performed, and four references were comments. A total of 120 papers involving 162 patient cases were used in our study.

Patient characteristics

The collected data on patient characteristics are shown in [Table 1]. Eighty-nine (55.6%) of the patients were female, the mean (SD) age of the patients at operation time was 34.3 (16.9) years, and CR was achieved in 98 (60%) of patients. The cyst was most reported as intradural (160 [98.8%]) and extra-axial (154 [95.1%]). The ventral craniocervical junction (CCJ) was the most common location for the cyst (46 [28.4%]) and the retrosigmoid approach was the most utilized surgical approach (68 [42.0%]). The mean (SD) length of the cystic lesion was 30.5 (13.5) mm and 87 (61.7%) patients had type A NCs.

Preoperative diagnostic imaging characteristics

A summary of the collected preoperative diagnostic images is shown in [Table 2]. CT scans reported the cyst mainly as hypodense in 32 (61.5%) of the patients. On MRI, the cyst was reported hyperintense in 66 (48.5%) patients on T1WI

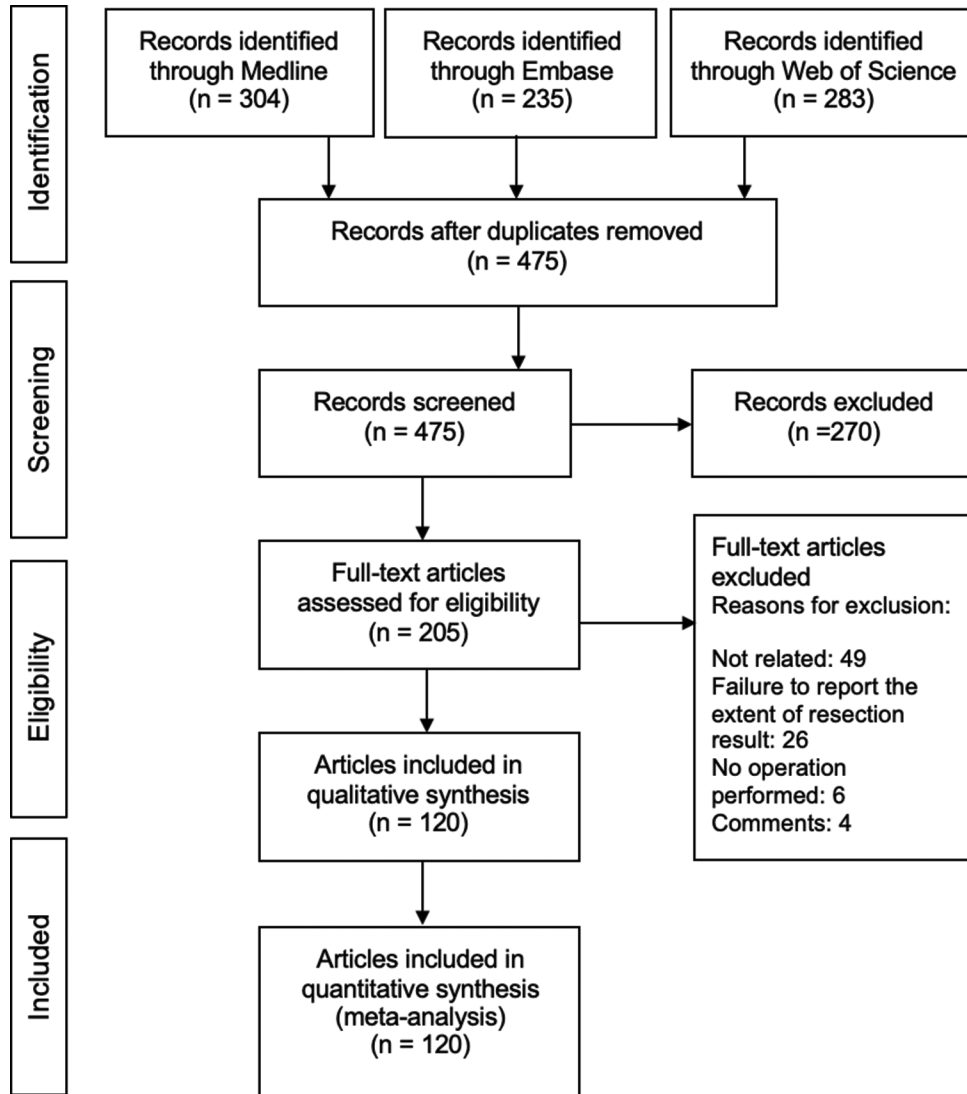


Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart of scientific literature search and study selection.

and hyperintense in 98 (67.1%) patients on T2WI. With contrast enhancement, 16 (61.5%) of the scans reported the cyst as hyperintense on T1WI and hyperintense in 10 (58.8%) of the scans in T2WI MRI. Hyperintense signals from the cyst were also mainly observed in 17 (63.0%) patients by fluid-attenuated inversion recovery.

Due to cases frequently reporting only one MRI sequence type, [Table 3] displays the data from cases reporting both signal intensities from T1WI and T2WI MRI. Isointense readings were excluded from the cross-tabulation. Out of the 89 patients who had both the T1WI and T2WI MRI scans, 45 (50.6%) reported the cyst as hyperintense on T1WI and hyperintense on T2WI MRI without contrast enhancement. Out of the 14 patients reporting contrast-enhanced MRI imaging, the cyst was mainly hypointense on T1-weighted and hyperintense on T2-weighted MRI (6 [42.9%]).

Factors associated with CR

Variables tested in the univariate logistic regression model are shown in [Table 4]. Cyst length, cyst type, and preoperative diagnostic images were not predictive of complete cyst resection. Univariate analysis showed male sex as a statistically significant predictor for complete reaction (OR 2.13, 95% CI 1.10–4.11, $P = 0.02$). The retrosigmoid approach (OR 1.89, 95% CI 0.98–3.63, $P = 0.06$), far lateral approach (OR 0.46, 95% CI 0.21–1.02, $P = 0.06$), and pediatric patient (OR 2.45, 95% CI 0.94–6.56, $P = 0.07$) may be possible predictors for CR, however, they were not statistically significant. All variables with $P < 0.25$ were selected in a multivariable logistic regression model, as shown in [Table 4]. $P = 0.25$ is recommended since more traditional levels such as 0.05 can fail in identifying variables known to be important.^[2] Male sex in the multivariable analysis was an independent factor for CR

Table 1: Patient demographics stratified by complete or incomplete cyst resection.

Variable	No. of patients with data available	All patients	IR	CR	P-value
Male	160	71 (44.4)	21 (32.3)	50 (51.5)	0.02
Pediatric (<18)	162	27 (16.7)	6 (9.38)	20 (12.3)	0.06
Age at op. time mean (SD), years	162	34.3 (16.9)	35.4 (14.9)	33.5 (18.1)	0.18
Intradural	162	160 (98.8)	62 (38.3)	98 (60.5)	0.15
Extra-axial	162	154 (95.1)	59 (36.4)	95 (58.6)	0.27
Cyst location	162				0.56
Ventral CCJ		46 (28.4)	15 (32.6)	31 (67.4)	
Lateral CCJ		12 (7.4)	7 (58.3)	5 (41.7)	
Dorsal CCJ		13 (8.0)	4 (30.8)	9 (69.2)	
Pontine cistern		22 (13.6)	7 (31.8)	15 (68.2)	
4 th ventricle		8 (4.9)	4 (50.0)	4 (50.0)	
Vermis		6 (3.7)	2 (33.3)	4 (66.6)	
Superior cistern		2 (1.2)	1 (50.0)	1 (50.0)	
CPA		34 (21.0)	13 (38.2)	21 (61.8)	
PMJ		18 (11.1)	10 (55.6)	8 (44.4)	
Intramedullary		1 (0.6)	1 (100.0)	0 (0.0)	
Cyst length mean (SD), mm	72	30.5 (13.1)	28.9 (12.3)	31.7 (13.5)	0.27
Resection Approach	162				0.36
Midline suboccipital		36 (22.2)	16 (44.4)	20 (55.6)	
Retrosigmoid		68 (42.0)	21 (30.9)	47 (69.1)	
Far lateral		31 (19.1)	17 (54.8)	14 (45.2)	
Transcondylar		8 (4.9)	3 (37.5)	5 (62.5)	
Endo nasal		5 (3.1)	3 (60.0)	2 (40.0)	
Transoral		4 (2.5)	1 (25.0)	3 (75.0)	
Presigmoid		7 (4.3)	3 (42.9)	4 (57.1)	
Supraorbital		1 (0.6)	0 (0.0)	1 (100.0)	
Occipital transtentorial		2 (1.2)	0 (0.0)	2 (100.0)	
Cyst type	141				0.89
A		87 (61.7)	37 (42.5)	50 (57.5)	
B		49 (34.8)	19 (38.8)	30 (61.2)	
C		5 (3.5)	2 (40.0)	3 (60.0)	
CT (excluding isointense)	48				0.37
W		17 (35.4)	10 (41.7)	7 (28.0)	
MRI (excluding isointense)					
T1 intensity	121				0.66
W		65 (53.7)	23 (52.3)	42 (54.5)	
T1 intensity (w/contrast)	23				0.65
W		16 (69.6)	6 (60.0)	10 (76.9)	
T2 intensity	101				0.73
W		82 (81.2)	31 (81.6)	51 (81.0)	
T2 intensity (w/contrast)	14				0.07
W		10 (71.4)	4 (50.0)	6 (100.0)	

CR: Complete resection, IR: Incomplete resection, CCJ: Craniocervical junction, CPA: Cerebellopontine angle, PMJ: Pontomedullary junction, W: Hyperintense/hyperdense

(OR 1.99, 95% CI 1.00–3.94, $P = 0.05$). The lateral CCJ may be a possible independent factor for CR, however, was not statistically significant (OR 0.44, 95% CI 0.13–1.44, $P = 0.09$)

DISCUSSION

To the best of our knowledge, this is the first meta-analysis and systematic review on posterior fossa NCs. Cyst

recurrence has been shown to occur greater in patients with IR,^[5,6,10,12,14] and therefore, CR should be always attempted. However, CR is not always possible as the cyst wall can tightly adhere to vital structures. Our univariate analysis demonstrated that male sex is a statistically significant predictor for CR. Pediatric patients, retrosigmoid approach, and far lateral approach may be associated with CR as well, however, none were significant. Our multivariable analysis

Table 2: Summary of all diagnostic images.

Imaging type	No. of patients with data available	All patients
CT	52	
B		32 (61.5)
G		3 (5.8)
W		17 (32.7)
MRI T1 w/o contrast	136	
B		56 (41.2)
G		14 (10.3)
W		66 (48.5)
MRI T1 w/contrast	26	
B		7 (26.9)
G		3 (11.5)
W		16 (61.5)
MRI T2 w/o contrast	146	
B		28 (19.2)
G		20 (13.7)
W		98 (67.1)
MRI T2 w/contrast	17	
B		4 (23.5)
G		3 (17.6)
W		10 (58.8)
FLAIR	27	
B		2 (7.4)
G		8 (29.6)
W		17 (63.0)

W: Hyperintense/hyperdense, G: Isointense/isodense, B: Hypointense/hypodense

Table 3: Cross-tabulation of T1- and T2-weighted imaging.

		T1WI		
		W	B	
T2WI	W	25 (28.1)	45 (50.6)	*Reported by 89 cases
	B	19 (21.3)	0 (0.0)	
		T1WI w/contrast		
		W	B	
T2WI w/contrast	W	4 (28.6)	6 (42.9)	*Reported by 14 cases
	B	4 (28.6)	0 (0.0)	

W: Hyperintense, B: Hypointense

demonstrates that male sex was an independent preoperative factor for CR. The lateral CCJ was identified as a possible predictor, however, was not significant. Due to the variation of appearance of NCs and their rareness in literature, they may be misdiagnosed on preoperative diagnostic images as cancerous tumors or cysts such as parasitic, arachnoid, dermoid, choroidal, or Rathke and colloid.^[20] To minimize these common misdiagnoses, we highlight the key features of NCs on diagnostic images that help discriminate from other intracranial lesions.

Cancerous tumors enhance strongly with gadolinium and are rarely located along the midline.^[25] NCs are most commonly situated at the midline and are typically unaffected by contrast enhancement, however, a slight rim enhancement is occasionally observed from the cyst wall.^[8,20-23] Parasitic cysts have a high signal on CT and MRI, occur as multiple lesions, and invade the surrounding matter similarly to cancerous tumors.^[4] T1WI intensity varies greatly for NCs, however, T2WI is also most often hyperintense. Unlike parasitic cysts, NCs occur almost always as a single lesion and do not invade the brain matter but rather compress the surrounding structures as they develop. Arachnoid cysts express hyperdensity on CT and isointensity on all MRI sequences and do not show any signs of restriction on diffusion-weighted imaging (DWI).^[17] NCs are mainly hypodense on CT and show mild restriction on DWI. Choroid cysts are commonly found along the choroid plexus and show strong restriction on DWI.^[13] Epidermoid and dermoid cysts are most difficult to differentiate from NCs as they also are commonly situated at the midline, rarely show enhancement from gadolinium, and are usually hypodense on CT. However, epidermoid and dermoid cysts commonly encase neurovascular structures^[15,16] whereas NCs are more likely to compress the adjacent structures. Greater restriction on DWI is also observed when compared to NCs. Rathke cysts are solely located on the sella turcica^[3] and colloid cysts are located in the interventricular foramen.^[11]

Using various diagnostic imaging methods including the use of contrast agents can help narrow down and identify the correct intracranial abnormality. A CT scan is necessary to exclude congenital bony anomalies or bone malformation which is often observed with NCs.^[19] Diffusion tensor imaging (DTI) tractography can be used for preoperative planning of cortical and subcortical brain tumor resection. It can also be used in some cases to help in the assessment of the origin of the cyst whether it is intra- or extra-axial. NCs will rarely occur extradural or intra-axial as shown from our study.

Surgical resection is currently the only effective treatment for patients with intracranial NCs and is recommended in symptomatic patients.^[5] NCs are benign and slow-growing lesions, and therefore, the surgical removal may impose a greater threat than the cyst itself. With 72.2–90% of intracranial NCs located in the posterior fossa, a craniotomy of the posterior fossa is almost always utilized. Posterior fossa surgery is not to be taken lightly as it is shown to carry an overall complication rate commonly including CSF leakage, meningitis, or wound infection of 31.8% and a 2.6% mortality rate.^[7] Complication and mortality rates could increase in patients undergoing additional operations due to cyst recurrence and therefore CR during the first operation should be always attempted if appropriate.

Table 4: Analysis of factors associated with complete resection with binary logistic regression.

Variable	OR (95% CI)			
	Univariate analysis	P-value	Multivariable analysis	P-value
Male	2.13 (1.10–4.11)	0.02	1.99 (1.00–3.94)	0.05
Pediatric (<18)	2.45 (0.94–6.56)	0.07	2.36 (0.84–6.59)	0.10
Intradural	0.0 (0.0–0.0)	1.0	NA	NA
Extra-axial	0.0 (0.0–0.0)	1.0	NA	NA
Cyst location				
Ventral CCJ	1.51 (0.74–3.10)	0.26	NA	NA
Lateral CCJ	0.44 (0.13–1.44)	0.18	0.33 (0.09–1.17)	0.09
Dorsal CCJ	1.52 (0.45–5.15)	0.50	NA	NA
Pontine cistern	1.47 (0.56–3.84)	0.43	NA	NA
4 th ventricle	0.0 (0.0–0.0)	1.0	NA	NA
Vermis	0.0 (0.0–0.0)	1.0	NA	NA
Superior cistern	0.0 (0.0–0.0)	1.0	NA	NA
Cpa	1.07 (0.49–2.33)	0.86	NA	NA
Pmj	0.48 (0.18–1.29)	0.15	0.50 (0.17–1.47)	0.21
Intramedullary	0.0 (0.0–0.0)	1.0	NA	NA
Cyst length, mm	1.02 (0.98–1.06)	0.32	NA	NA
Resection approach				
Midline suboccipital	0.77 (0.36–1.63)	0.49	NA	NA
Retrosigmoid	1.89 (0.98–3.63)	0.06	1.62 (0.75–3.48)	0.22
Far lateral	0.46 (0.21–1.02)	0.06	0.54 (0.21–1.36)	0.19
Transcondylar	0.0 (0.0–0.0)	1.0	NA	NA
Endo nasal	0.0 (0.0–0.0)	1.0	NA	NA
Transoral	0.0 (0.0–0.0)	1.0	NA	NA
Presigmoid	0.0 (0.0–0.0)	1.0	NA	NA
Supraorbital	0.0 (0.0–0.0)	1.0	NA	NA
Occipital transtentorial	0.0 (0.0–0.0)	1.0	NA	NA
Cyst type				
A	0.92 (0.46–1.85)	0.81	NA	NA
B	0.97 (0.48–1.98)	0.93	NA	NA
C	0.0 (0.0–0.0)	1.0	NA	NA
CT (excluding isointense)				
W	0.54 (0.17–1.79)	0.317	NA	NA
MRI (excluding isointense)				
T1 intensity (w/o contrast)				
W	1.18 (0.56–2.47)	0.66	NA	NA
T1 intensity (w/contrast)				
W	2.22 (0.37–13.5)	0.39	NA	NA
T2 intensity (w/o contrast)				
W	1.1 (0.40–2.98)	0.86	NA	NA
T2 intensity (w/contrast)				
W	0.0 (0.0–0.0)	1.0	NA	NA

CCJ: Craniocervical junction, CPA: Cerebellopontine angle, PMJ: Pontomedullary junction, W: Hyperintense/hyperdense

Limitations

When studying rare medical conditions, the main limitation often arises from the lack of data found in the literature. The extractable data on intracranial NCs were limited to single case reports and case series typically consisting of less than 10 patients. In addition, the data reported from each case differed in robustness, and therefore, statistical analyses were limited to only the variables commonly reported. This study

analyzed only the first operation undergone by patients so statistical findings may not correlate to patients undergoing additional operations.

Future directions

Incorporating additional diagnostic imaging methods such as DWI, DTI tractography, and the use of contrast agents may help to correctly diagnose NCs preoperatively and identify

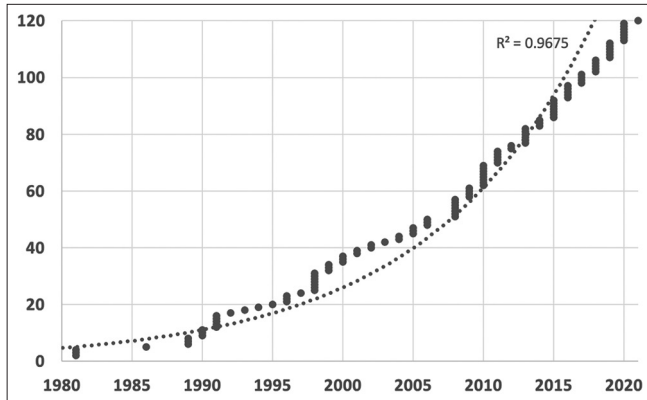


Figure 3: Scientific reports on posterior fossa neurenteric cysts overtime with a best-fit curve.

the cyst location with greater precision. Findings from our statistical analysis on NCs and general characteristics on diagnostic imaging may require additional reports in the future to strengthen these findings and to test other possible variables that may influence resection outcomes. As shown in [Figure 3], reports on NCs are increasing rapidly and may be due to the advancements of diagnostic imaging methods. We strongly encourage future reports to carefully mention all data presented by patients including all pre- and postoperative diagnostic images.

CONCLUSION

CR of posterior fossa NCs is moderately achievable shown by 60% of all cases reported. The cyst is slightly more common in females, and the male sex is independently associated with CR. Diagnostic images show that NCs are mainly hypodense on CT, hyperintense on T2WI and show high variability on T1WI.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Pettersson SD, Ali S, Burmaka P, Fercho J, Szmuda T, Abuhaimed A, *et al.* Predictors for complete surgical resection of posterior fossa neurenteric cysts: A case report and meta-analysis. *Surg Neurol Int* 2021;12:530.