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Epidemiology and Clinicopathologic Study of Nonneoplastic Cystic Lesions of the Central Nervous System at a Tertiary Care Center

Mukesh Kumar[1] Mukta Meel[2] Nikita Choudhary[2] Ashok Singh[2] Kusum Mathur[2]

[1] Department of Neurosurgery, SMS Medical College, Jaipur, Rajasthan, India
[2] Department of Pathology, SMS Medical College, Jaipur, Rajasthan, India

Address for correspondence Mukta Meel, MBBS, MD, Department of Pathology, SMS Medical College, Jaipur 302004, Rajasthan, India (e-mail: drmuktab@yahoo.com).

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Abstract

Background Nonneoplastic cysts of brain are a diverse group of benign lesions with variable etiopathogenesis. Due to different site and histogenesis, these lesions have wide clinicopathologic spectrum.

Objective The study was performed to evaluate epidemiology and clinicopathologic spectrum of nonneoplastic central nervous system (CNS) cysts highlighting the role of histopathology in the diagnosis as well as to compare the data with other institution's data available in literature.

Materials and Methods All nonneoplastic CNS cysts reported from January 2013 to June 2020 in the Department of Pathology of Sawai Man Singh Medical College, Jaipur, were retrieved and reviewed. The data were evaluated for age, site, cyst wall lining, nature of cyst contents, and location (intracranial and spinal), using SPSS software version 20.0.

Results A total of 255 cases were reviewed with an incidence of 4.96% and an age range of 2 to 74 years with slight male preponderance. Among them there were 157, 34, 26, 24, and 2 cases of epidermoid, arachnoid, dermoid, colloid, and glioependymal cysts, respectively, and 1 case of perineural cyst. Infective cysts were much less common than noninfective cysts, accounting for two cases of neurocysticercosis and hydatid cysts each. All cyst types mainly presented with signs and symptoms of a mass lesion.

Conclusion Nonneoplastic cyst mainly presented like a CNS mass lesion with overlapping clinical features, and image finding revealing the key role of histopathological analysis. Epidermoids were the most common type of these cysts in the present series followed by the arachnoid cysts.

Keywords
- clinicopathologic spectrum
- histopathology
- nonneoplastic cysts of brain

Introduction

A true cyst can be defined as an abnormal closed epithelium-lined sac in the body that contains a liquid or semisolid substance while a pseudo cyst or false cyst is an abnormal or dilated cavity resembling a true cyst but not lined with epithelium.[1] Intracranial cystic lesions are divided into two types: normal variants, such as cavum septi pellucidi, cavum veli interpositi, and cavum vergae, and developmental or congenital lesions.[2]

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These congenital nonneoplastic cystic lesions of the central nervous system (CNS) are uncommon, mostly benign, and discovered incidentally during routine radiological examination or at autopsy.[3] However, they become symptomatic either because of pressure, rupture, or secondary inflammation. On neuroimaging these may mimic with cystic neoplastic lesions, causing difficulty in accurate diagnosis. Meanwhile, there is no uniform terminology and classification scheme to make a consistent diagnosis among pathologists, neurosurgeons, and neuroradiologists. Though generally of good prognosis, they may recur due to rupture or incomplete surgical removal. The age, site, cyst wall, and cyst contents provide an insight into their histogenesis and embryology. In this study, we evaluated epidemiology and clinicopathologic spectrum of nonneoplastic CNS cysts that presented as symptomatic space-occupying lesions and highlighted the role of histopathology in the diagnosis of these cystic lesions. We also compared our data with other institution's data available in literature.

This is the second largest series studying all the nonneoplastic cystic lesions of the CNS, both developmental and acquired (►**Table 1**).

Materials and Methods

The present study was a retrospective analysis of the data on nonneoplastic cystic lesions of CNS, which involved the archival tumor blocks and clinicopathological data, submitted to the Department of Pathology of our Institution—Sawai Man Singh (SMS) Medical College, Jaipur—between January 2013 and June 2020. All neoplastic cystic lesions were excluded from the study. The age, site, cyst wall lining, nature of cyst contents, and location (intracranial and spinal) were noted in all cases for analysis. These included epidermoid cysts, dermoid cysts, arachnoid cysts, colloid cysts, glioependymal cysts, perineural cyst, benign cystic lesions (cysts that could not be classified under above categories), hydatid cysts, and neurocysticercosis.

All collected data were analyzed on SPSS software version 20.0. For continuous variables, mean value was calculated. Frequency and percentage were calculated for categorical variables. Since this was a retrospective observational study, ethical approval was not sought.

Results

During the study period of 7 and ½ years, a total of 255 histologically confirmed nonneoplastic cystic lesions were reviewed with an incidence of 4.96% (255/5,142 tumor and tumor-like lesions). Noninfective cysts were much more common (251/255) than infective cysts (4/255). Epidermoid cysts were the commonest, followed by arachnoid cysts, then dermoid cysts, and this was closely followed by colloid cysts of the third ventricle. Among infective cysts, two were hydatid cysts and two were neurocysticercosis (►**Fig. 1**).

The age range was 2 to 74 years (mean, 28.9 years) with slight male preponderance (male:female [M:F] ratio = 1.15:1; ►**Table 1**; ►**Fig. 2**).

Majority of intracranial cysts had signs of raised intracranial pressure. Patients with epidermoid cysts had additional cerebellar signs, visual disturbances, and deafness due to their posterior fossa location. The spinal cysts of all types presented with cord compression leading to lower limb weakness. The epidermoid and arachnoid cysts were more common in the brain, while dermoid cysts in the spinal cord.

Among all nonneoplastic cystic lesions, epidermoid cysts were the most common and constituted 61.6% (157/255). The overall age range was 4 to 65 years with a mean age of presentation being 30 years and M:F ratio, 1.24:1. In males, age range was 4 to 63 years, while in females; it was 10 to 65 years. Intracranial location was more common (78.3%) than spinal one (21.7%). Most common intracranial site was posterior fossa (49.6%), followed by cerebral hemispheres (30.1%). Equal incidence was found in ventricles and suprasellar site (5.7%). Other intracranial sites were pineal (2.4%); interhemispheric and middle cranial fossa base (1.6% each); and anterior cranial fossa base, brain stem, basal cistern, and quadrigeminal cistern (0.8% each). With the cerebral hemispheres, temporal lobe (40.5%) was the most common, followed by frontal lobe (21.6%). Intraspinal cysts were more frequent in lumber (58.8%) location followed by thoracolumbar (20.6%), thoracic (14.8%), and cervical and lumbosacral (2.9%, each). Of these, 38.2% were intramedullary and 61.8% were intradural–extra medullary (►**Table 2**). Histologically, these cysts were lined by keratinized stratified squamous epithelium and cyst wall composed of fibrocollagenous connective tissue without skin appendages. Lumen was filled with acellular lamellated keratinous flakes (►**Fig. 3A**). Abscess formation was seen in two of the cases and foreign body giant cell reaction was noted in seven cases.

Second most common cysts were arachnoid cysts constituting 13.3%, with an age range of 3 to 72 years and mean age 31 years. Among those, 21 were male patients while female patients were 13 with an M:F ratio of 1.62:1 (►**Fig. 2**). Out of 34 cases, 22 (64.7%) were intracranial and remaining 12 (35.3%) were intraspinal. In cranium locations were posterior fossa (12), ventricular (5), intraparenchymal (4), and sellar (1). In spine locations were thoracic (6), cervical (3), lumber (2), and cervicothoracic (1 [►**Table 2**]). These cysts presented with pressure symptoms. In histology, cysts were lined by flattened meningothelial (arachnoidal) cells supported by collagenous cyst wall. The contents of these cysts were clear fluid, like cerebrospinal fluid (CSF; ►**Fig. 3B**).

There were 26 cases (10.2%) of dermoid cysts located predominantly in spine (69.2%; 66.7% in lumber). Intracranial compartment accounted for 30.8% of lesions and hemispheric location was most common (75%; ►**Table 2**). Out of total 18 cases of spinal region, 13 cases were intradural–extra medullary while remaining 5 cases were intramedullary. The age range was 2 to 62 years and mean age of presentation was 23 years (►**Table 1**). Male predilection was seen in these with an M:F ratio of 4.2:1 (►**Fig. 2**). Histologically, these cysts were lined keratinized stratified squamous epithelium with hair follicles, sweat, and sebaceous glands in cyst wall. The contents included keratin flakes, hair, or sebum (►**Fig. 3C**).

Table 1 Demographic details for all histological types as well as comparison with national data

Diagnosis	SMS, Jaipur ($n = 255$)				NIMHANS, Bangalore**6** ($n = 538$)				GB Pant Hospital, New Delhi**7** ($n = 109$)			
	Age range (y)	Mean age (y)	M:F ratio	Frequency (%)	Age range (y)	Mean age (y)	M:F ratio	Frequency (%)	Age range (y)	Mean age (y)	M:F ratio	Frequency (%)
Epidermoid cyst	4–65	30	1.24:1	61.6	3–64	33.37	1.04:1	24.5	NA	NA	NA	31.2
Colloid cyst	9–66	28	1.4:1	9.4	9–90	34.7		23.4	NA	NA	NA	14.7
Arachnoid cyst	3–72	31	1.62:1	13.3	5 months to 66 years	29.5	1.01:1	20.6	NA	NA	NA	24.8
Dermoid cyst	2–62	23	4.2:1	10.2	2–54	22.24	2.2:1	6.1	NA	NA	NA	15.6
Benign cystic lesion	7–74	31	2.5:1	2.7	3–66	32.7		2	NA	NA	NA	NA
Glioependymal cyst	38–42	40	–	0.8	6 months to 59 years	14.35	2.3:1	1.9	NA	NA	NA	2.7
Perineural cyst	18	18	–	0.4	21–75	42.6	1.6:1	1.5	NA	NA	NA	NA
Rathke's cleft cyst	NA	NA	–	0.8	12–77	43.03	1:01	5.6	NA	NA	NA	2.8
Neuroenteric cyst	NA	NA	–	0.8	2–74	23.5	2.25:1	4.8	NA	NA	NA	7.3
Porencephalic cysts	NA	NA	–	NA	5–34	21.33	1:02	0.6	NA	NA	NA	NA
Neurocysticercosis	42–48	45	–	NA	6–68	33.8	1.2:1	7.8	NA	NA	NA	NA
Hydatid cyst	12–29	20	–	NA	10–48	27.4	1:01:03	1.3	NA	NA	NA	NA

Abbreviations: GB, Govind Ballabh; NA, not available; NIMHANS, National Institute of Mental Health and Neuro-Sciences; M:F, male to female ratio; SMS, Sawai Man Singh (Medical College).

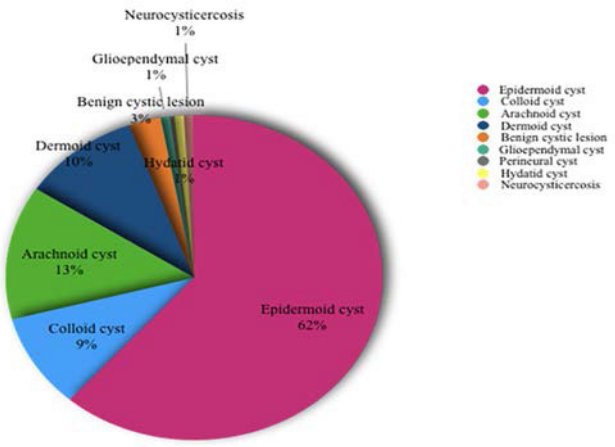

Fig. 1 Overall distribution of nonneoplastic cystic lesions of central nervous system.

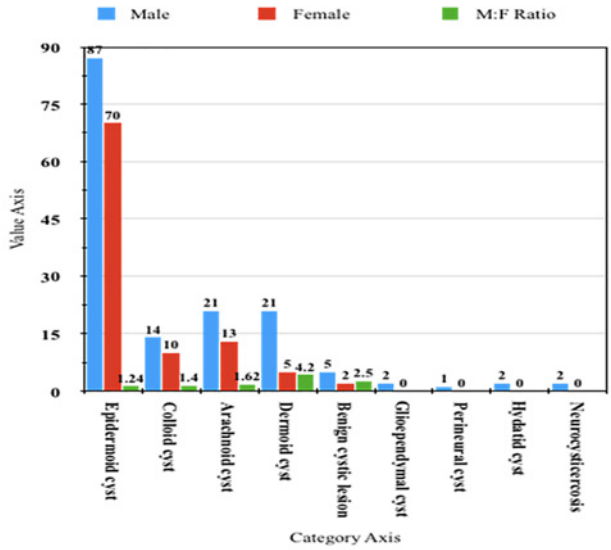

Fig. 2 Number of male and female patients as well as male to female ratio for all histological subtypes of nonneoplastic cystic lesions of central nervous system.

Colloid cysts constituted 9.4% (24/255) of total cases. For these, overall age range was 9 to 66 years with a mean age of 28 years and M:F ratio of 1.4:1. All cases were located in the third ventricle except one, which was in the posterior fossa (►**Table 1** and ►**Table 2**). Morphologically these cysts were lined by cuboidal to columnar epithelium with or without cilia, supported by delicate collagenous stroma and colloid-like material in the lumen, which showed periodic acid–Schiff positivity (►**Fig. 3D**). There was hemorrhage with hemosiderin laden macrophages and xanthogranulomatous reaction in five cases.

Less frequently occurring cysts were glioependymal cysts (two cases) and perineural/Tarlov's cyst (one case). Both glioependymal cysts were found in males of age 38 and 42 years. One was in posterior fossa of intracranium and one was in thoracic region of spine. Microscopically, these cysts were lined by cuboidal to columnar ependymal cells resting on glial tissue (►**Fig. 4A**). The single perineural cyst in our series was found in an 18-year-old male in sacral region of spine. They were characterized by the presence of nerve bundles in the cyst wall (►**Table 2**).

Only 4 cases of infective cysts were encountered; 2 were of hydatid cysts in males of age 12 and 29 years and 2 were of neurocysticercosis in males of age 42 and 48 years. Both cases of hydatid cysts were located in cerebral hemispheres, parietal and occipital; while location of neurocysticercosis was cerebellum and frontal hemisphere. Microscopically, neurocysticercosis cases were in cystic/vesicular stage and showed membrane of the cyst showing outer layer covered with microvillus (►**Fig. 4B**). Morphologically, hydatid cysts were characterized by presence of lamellated membranes (►**Fig. 4C**). In our series, seven cases were put in benign cystic lesion category due to the absence of specific features of any of the above cystic lesions, in particular, an indistinct lining.

However, there was no case of neuroenteric cyst, Rathke's cleft cyst, or porencephalic cyst in the current series.

We also compared clinical parameters as mean age and frequency percentage of cystic lesions with Indian data: National Institute of Mental Health and Neuro-Sciences (NIMHANS) and Govind Ballabh (GB) Pant Hospital data (►**Table 1**). In all types of cystic lesions, epidermoid cysts were most common in all above institutions, but frequency percentage was different. Second common cysts were arachnoid cysts in our study similar to GB Pant data, but in NIMHANS colloid cysts were second most common. For almost all histologies, the mean age at diagnosis was similar between the SMS Medical College and NIMHANS data, marginally varying by just 2 to 4 years for most lesions.

Discussion

Cysts of CNS are usually diagnosed radiologically and confirmed histologically. They show wide variety of histomorphology. Exact typing of these lesions is crucial and depends on type of the lining of the cyst wall and anatomical location, as it is essential for treatment and has prognostic importance.

Epidermoid cysts are uncommon congenital lesions that account for 0.2 to 1.8% of all intracranial tumors and less than 1% of all intraspinal tumors.[4] They result from inclusion of ectodermal elements during neural tube closure between the third and fifth weeks of fetal development, and typically present in middle age due to mass effect on adjacent structures. Less commonly, the cysts may develop later in life (acquired) when an injury or surgery causes epithelial cells to be trapped in brain tissue.[5] Mean age of presentation for epidermoid cysts was 30 years similar to the study done by Bhatt et al, and M:F ratio was 1.24:1 showing slight male preponderance.[6] Upon comparison on location, intracranial epidermoid cysts were more common than spinal one with a ratio of 14:1.1 to 3. The current series showed an approximate ratio of 3.62 similar to the studies done by Sidhu et al (3.25:1) and Sundaram et al (5:1).[7,8] Most common site in intracranial compartment was posterior

Table 2 Location of noninfective nonneoplastic cysts of central nervous system

Type of cysts	Number of cases	Location	Number of cases
Epidermoid cysts	157		
Intracranial	123/157	Parenchymal	37
		Inter hemispheric	2
		Sellar and suprasellar	7
		Pineal	3
		Anterior cranial fossa base	1
		Middle cranial fossa base	2
		Posterior fossa	61
		Brain stem	1
		Ventricles	7
		Basal cistern	1
		Quadrigeminal cistern	1
Spinal	34/157	Cervical	1
		Thoracic	5
		Thoracolumbar	7
		Lumber	20
		Lumbosacral	1
Dermoid cysts	26		
Intracranial	8	Parenchymal	6
		Sellar	1
		Posterior fossa	1
Spinal	18	Cervical	1
		Thoracic	1
		Thoracolumbar	2
		Lumber	12
		Lumbosacral	1
		Sacral	1
Colloid cysts	24		
Intracranial		Third ventricle	23
		Posterior fossa	1
Arachnoid cysts	34		
Intracranial	22	Intraparenchymal	4
		Sellar	1
		Ventricular	5
		Posterior fossa	12
Spinal	12	Cervical	3
		Cervicothoracic	1
		Thoracic	6
		Lumber	2
Benign cystic lesion	7		
Intracranial	5	Intraparenchymal	1
		Sellar	3
		Ventricle	1

Table 2 (*Continued*)

Type of cysts	Number of cases	Location	Number of cases
Spinal	2	Lumbosacral	1
		Sacrococcygeal	1
Glioependymal cysts	2		
Intracranial	1	Posterior fossa	1
Spinal	1	Thoracic	1
Perineural cyst	1		
Spinal	1	Sacral	1

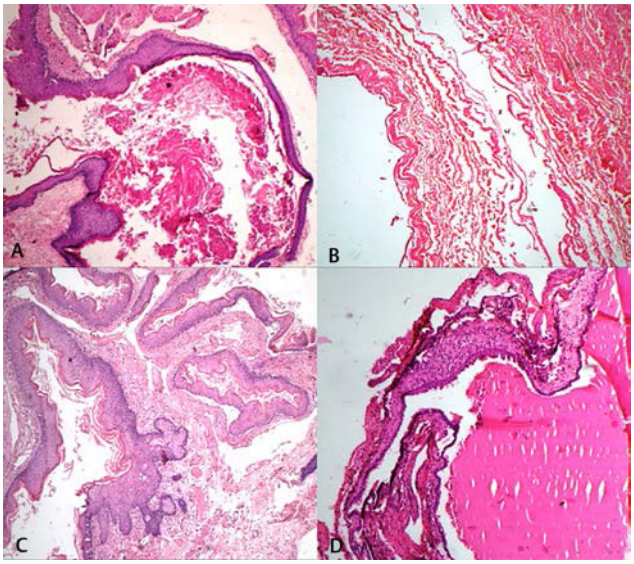

Fig. 3 (**A**) Epidermoid cyst showing keratinized stratified squamous epithelium and acellular lamellated keratin. (**B**) Arachnoid cyst showing a single layer of flattened meningothelial cells resting on fibrocollagenous connective tissue. (**C**) Dermoid cyst showing keratinized stratified squamous epithelium and pilosebaceous unit in the cyst wall. (**D**) Colloid cyst lined by columnar cells with eosinophilic acellular material as cyst content.

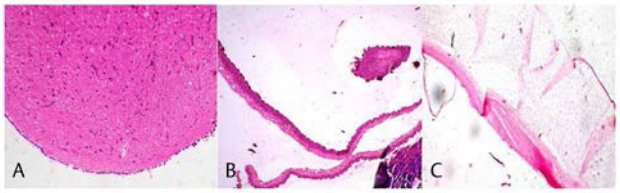

Fig. 4 (**A**) Glioependymal cyst lined by low cuboidal type epithelium resting in glial tissue. (**B**) Neurocysticercosis showing cystic stage. (**C**) Hydatid cyst showing lamellated membrane.

fossa (49.5%) and cerebellopontine angle (42.2%), similar to other studies, followed by cerebral hemispheres (30.1%). Other sites were ventricular region, pineal, sellar and suprasellar, interhemispheric, base of anterior cranial and middle cranial fossa, and basal and quadrigeminal cistern. We also encountered a single case of brain stem epidermoid, which is extremely rare.[8–10] In cerebral hemispheres, temporal lobe was most commonly (15 cases) involved followed by frontal lobe (8 cases). In intraspinal epidermoid cysts, most common location was lumber followed by thoracolumbar and thoracic.

In the present series, the second most commonly encountered cyst was arachnoid cysts similar to the report by Sidhu et al.[7] They can be of two types: primary arachnoid cysts, which are congenital, and secondary cysts, resulting from head injury or trauma.[11,12] They are CSF covered by arachnoid cells and collagen that may develop between the surface of the brain and the cranial base, or on the arachnoid membrane, one of the three meningeal layers that cover the brain and the spinal cord.[13,14] The mean age of presentation was 31 years, similar to the study performed by Bhatt et al where mean age was 29.5 years.[6] Arachnoid cysts were founded more commonly in males, similar to the study by Al-Holou et al, and M:F ratio was 1.62:1. Intracranial arachnoid cysts were more common (64.7%) than spinal ones (35.3%), similar to the studies by Sidhu et al and Bhatt et al.[6,7,15] In the spine, lumber region was the commonest location, concordant with Sundaram et al.[8] The spinal arachnoid cysts are located subdurally and are true arachnoid cysts.

Dermoid cysts constituted 10.2% of all nonneoplastic cystic lesions, and were the third most common lesion in our series similar to the study by Sidhu et al.[7] They are mal-developmental and a result of the inclusion of ectoderm during neural tube closure similar to epidermoid cysts. The median location of these tumors can be explained by the separation of neuroectoderm and its cutaneous counterpart that occurs dorsally along the midline. However, during the formation of secondary otic and optic cerebral vesicles, inclusion of ectoderm at a later stage of embryogenesis leads to lateral location of these lesions.[9,16–18] They were found more commonly in males with a mean age of 23 years, similar to the studies conducted by Din et al and Bhatt et al.[3,6] Like other studies, mean age for dermoid cysts was younger compared with that for epidermoid cysts (23 years compared with 30 years). Similar to other studies, they were predominantly intraspinal (69.2%) in contrast to epidermoid cysts, with a preferential location in lumber region.[3,6,7]

Colloid cysts are well-defined clinicopathologic entity and easily identified on radiological imaging due to high cholesterol content.[19] They usually present with symptoms

of raised intracranial tension resulting from acute hydrocephalus by obstruction of one or both foramina of Monro due to their specific site of third ventricle. Regarding origin of these cysts, there are studies that denote their endodermal origin rather than a neuroepithelial one, as the epithelium of colloid cysts is immunohistochemically different from normal or neoplastic choroid epithelium.[8,20,21] Similar to other studies, males were affected more commonly than females and commonly in third decade of life. They were fourth commonest cysts in the series, similar to the report by Sidhu et al.[7] We encountered only two cases of glioependymal cysts in the current series. According to Friede and Yasargil, these cysts arise from displaced segments of the wall of the neural tube that correspond to the sites from which tela choroidea forms.[22] Histologically, these cysts are lined by columnar or cuboidal epithelium resting directly on brain parenchyma without a basement membrane and connective tissue. They formed 0.8% of the series. Only a single case of perineural cyst or Tarlov's cyst was present in the series in sacral region. They are located along the nerve roots in perineural space between the perineurium formed by arachnoid and pia mater.[23]

On computed tomography scan most of the noninflammatory cysts appear as well-circumscribed lesions, being iso- to hypodense, without contrast enhancement, except colloid cyst, which appears hyperdense with peripheral enhancement. On magnetic resonance imaging, they have minor differences. Arachnoid cysts and glioependymal cysts have same signal intensity in T1- and T2-weighted images as CSF and no contrast enhancement. Epidermoid cysts show low signal in T1-weighted and high signal in T2-weighted sequences and demonstrate restricted diffusion on diffusion-weighted mages. Dermoid cysts appear hyperintense in T1-weighted and hypo- to hyperintense in T2-weighted sequences. Colloid cyst appears hyperintense in T1-weighted and hypointense in T2-weighted imaging with peripheral contrast enhancement. However, cystic neoplasms differ from noninflammatory cysts by vasogenic surrounding edema and their solid part show contrast enhancement.[24–28]

In our series, we were not able to categorize five intracranial and two spinal cysts into any category and so put them as a benign cystic lesion because there was no distinct cell lining and no clue of cyst contents. It may be due to a small biopsy tissue submitted in our department as soft tissue pieces without any content and their lining was also not well demarcated to put them in any of the cyst categories, but they were showing a cyst wall without any mitotic and neoplastic pathology. Immunohistochemical or ultrastructural studies may help in such cases. These benign cysts of the CNS are being recognized more frequently with the advent of modern neuroimaging. They are usually mal-developmental, and malignant transformation of the lining epithelium is extremely rare.

In the present series, there were only four cases of infective cystic lesions. Two cases were of neurocysticercosis and two were of hydatid cysts. Neurocysticercosis is the infection of CNS caused by the *Taenia solium* (pork tapeworm). It can be intraparenchymal (benign) and extraparenchymal (malignant).[29] Location for extraparenchymal neurocysticercosis is the subarachnoid space and basal cistern. There are four morphological stages of neurocysticercosis, namely: vesicular stage, which lacks inflammatory reactions; vesicular colloidal state, wherein inflammation sets in; granular nodular stage, where the parasite is dead and degeneration starts; and, finally, the nodular calcified stage, wherein the parasite and the capsule are retracted and calcified.[30] In the current study, both cases of neurocysticercosis were intraparenchymal: one cerebral hemisphere and other cerebellum.

We encountered two cases of intracranial hydatid cysts, both in cerebral hemispheres: parietal and occipital. Intracranial hydatid cysts are much more common with an incidence of 1 to 2% than spinal hydatidosis.[6] The parietal lobe was found to be most commonly involved in studies by Dharker et al and Balasubramaniam et al.[31,32] Usually intracranial hydatid cysts are solitary and spread by hematogenous route.

Both infective cystic lesions in neuroimaging may mimic with other lesions depending on their location, as hydatid cyst of pineal region may be confused with pineocytoma, or ventricular region may mimic with choroid plexus tumors. Similarly, neurocysticercal cysts may mimic abscess, tuberculomas, neoplasms (both primary and metastatic, depending on the age of presentation), and other parasitic infections. Hence, a histopathological diagnosis becomes necessary in such cases for making an accurate diagnosis.

On comparing, majority of our data regarding mean age of presentation corroborates with similar data within India with minor differences, and epidermoid cysts were the most common among all nonneoplastic cystic lesions.

Conclusion

A variety of cystic lesions occurs in the CNS and presents as mass lesion. They have overlapped clinical features and imaging findings leading to problem in proper diagnosis. Morphology of cyst walls has a direct impact on further management, therefore histopathology has a vital role in diagnosis of these lesions. Our study is reinforcing the existing literature for the role of histopathology in the management of nonneoplastic cystic lesions of CNS.

Ethical Approval

Not required, as this was a retrospective analysis of brain tumors that involved the archival tumor blocks and clinicopathological data and did not involve any patient's personal information or any implication on the management protocol. Hence, according to the principles of the Helsinki Declaration, no ethical approval required.

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None.

Conflict of Interest

None declared.

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