

Research Paper: Endoscopic Surgical Management of Intracranial Symptomatic Arachnoid Cyst



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ABSTRACT

Background and Aim: Intracranial Arachnoid Cysts (IAC) are suitable choices for endoscopic procedure to avoid craniotomy or shunt placement. Our main objective is to study the outcome of endoscopic procedure in IAC treatment.

Methods and Materials/Patients: In this descriptive and retrospective study, we report our experience of 27 symptomatic patients with IAC who underwent endoscopic surgery at National Institute of Neurosciences Hospital and Dhaka Medical College Hospital, Dhaka, Bangladesh from January 2009 to December 2016. The recorded data of patients' management including operations, outcomes, and follow up were studied retrospectively. The diagnosis was confirmed by neuroimaging, surgery and histopathological examination. Patients were postoperatively followed up on regular basis.

Results: Size of the IAC decreased (significant to minimal) in all cases. Even where size reduction was minimal, patients' symptoms improved significantly. No IAC increased in size after endoscopic procedure. There was no recurrence of symptoms in the follow up period. There was no postoperative mortality or major morbidity related to the surgery.

Conclusion: Based on our results, most of symptomatic IAC cases can be managed by endoscopic procedure which seems to be a safe and effective method.

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Highlights

- Intracranial Arachnoid Cysts (IACs) are suitable candidates for endoscopic procedure
- Size of the IAC decreased (significant to minimal) in all studied cases after endoscopic intervention.
- Even where size reduction was minimal, patients' symptoms improved significantly.
- There was no recurrence of symptoms in the follow up period.
- There was no postoperative mortality or major morbidity.
- Most of the symptomatic IAC cases can safely and effectively be managed by endoscopic procedure

Plain Language Summary

Intracranial Arachnoid Cysts (IACs) are CSF containing cysts encased in arachnoid membrane that may produce clinical symptom/s. Symptomatic ones requires surgical treatment. IACs are suitable choices for endoscopic procedure to avoid open craniotomy or shunt placement. Here, the outcome of endoscopic procedure in IAC treatment was studied retrospectively. We report our experience of 27 symptomatic patients with IAC who underwent endoscopic surgery at National Institute of Neurosciences Hospital and Dhaka Medical College Hospital, Dhaka, Bangladesh from January 2009 to December 2016. The recorded data of the patients' management, including operations, outcomes, and follow up were studied retrospectively. The diagnosis was confirmed by neuroimaging, surgery and histopathological examination. Patients were postoperatively followed up on regular basis. Size of the IACs decreased (significant to minimal) in all cases. Even where size reduction was minimal, patients' symptoms improved significantly. There was no recurrence of symptoms or increase in the size of the cyst in the follow up period. There was no postoperative mortality or major morbidity related to the surgery. Based on our results, most symptomatic IAC cases can safely and effectively be managed by endoscopic procedure.

1. Introduction

Intracranial cysts are one of the most common conditions presented to neurosurgeons. They can be congenital or acquired [1, 2]. The most common intracranial cyst is arachnoid cyst [3]. Intracranial Arachnoid Cysts (IAC) are benign cystic lesions filled with Cerebrospinal Fluid (CSF), enclosed in arachnoid-like membrane [4]. Most arachnoid cysts remain asymptomatic throughout the life [5]. The prevalence of arachnoid cyst in children is 2.6% and in adults 1.4% [6-8].

The clinical manifestations depend on the location and size of the cyst [4]. They are incidental findings on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) performed for other reasons such as trauma [5]. In symptomatic patients, many treatments are available [4]. In the present era of minimally invasive neurosurgery, an endoscopic procedure for an IAC makes the treatment easier and safer [3]. This study aims to investigate the outcome of endoscopic treatment in

IAC. Here we also studied the other observational data related to the surgical management of IAC.

2. Methods and Materials/Patients

In this descriptive retrospective study, we report our experience of 27 symptomatic patients of IAC who underwent endoscopic surgery from January 2009 to June 2016 in the department of Neurosurgery, National Institute of Neurosciences Hospital and Dhaka Medical College Hospital, Dhaka, Bangladesh. As patients of IAC can be symptomatic or asymptomatic, asymptomatic patients were informed of their situation, assured and followed.

Symptomatic patients were evaluated to be certain that the symptoms were due to the cyst both clinically and radiologically. Thus, patients were evaluated and investigated accordingly prior to surgery. In all patients, we collected data regarding age, sex, symptoms at presentation, indication for imaging, location of intracranial arachnoid cyst, treatment modality used, and outcome of patients were taken retrospectively from recorded patients' files.

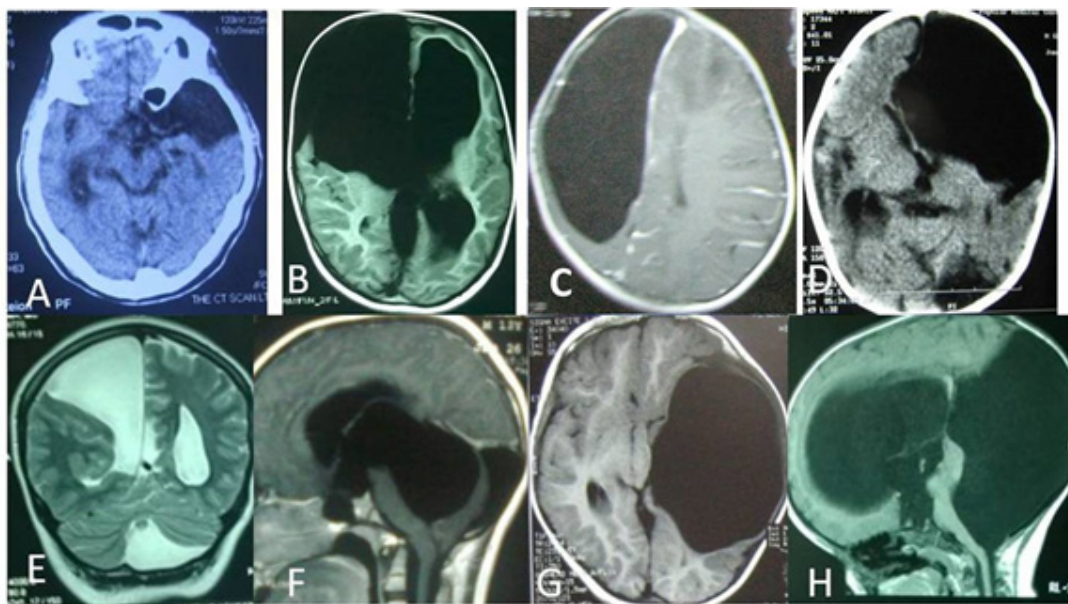


Figure 1. CT and MRI images of different types of IAC

A: Anterior temporal IAC; B: Frontal both extra- and intra-dural IAC; C: Frontal IAC; D: Large frontotemporal IAC; E: Parasagittal (parafalcine) IAC; F: Supracerebellar (pineal) IAC; G: Temporoparietal IAC; and H: Posterior fossa IAC with extension to supratentorial compartment.

In all patients, the diagnosis was confirmed by neuroimaging, during surgery and histopathological examination. The patients were postoperatively followed up clinically and radiologically (CT scan or MRI of brain) on regular basis and their recorded follow up data were studied. The patients, who were lost from follow up within 6 months after operation, were excluded from this study.

3. Results

A total of 27 patients with IAC underwent surgery. The patients' follow up period was between 9 to 89 months

(average 18.5 months). Fourteen patients were males and 13 were females, the mean age at the time of surgery was 14.7 years (range between 4 months and 5 years). Eight cases were below 12 months old. Eighteen cases were under 15 years old. Of the 27 IACs, 20 were in the supratentorial region, 4 in the infratentorial and 3 were both supra- and infra-tentorial regions (i.e. These IAC were extended from posterior fossa to the third and lateral ventricles through pineal region; tentorium cerebelli seemed to be intact but elevated). All IAC cases were intradural except one where the cyst was partially extradural (Figures 1, 2, and 3). Twelve patients had

Table 1. Clinical features of IAC cases before and after operation (n=27)

Clinical Features of IAC	No. (%)	
	Before Operation	After Operation
Headache	14 (51.8)	11(40.7)
Hydrocephalus	12(44.4)	12(44.4)
Head asymmetry (Figure 2)	4	0(0)
Epilepsy	1	1(100)
Gait disturbance	5	4(80)
Limb weakness	1	1(100)
Visual disturbances (Figure 6)	2	1(50)

Table 2. Age, sex, site of IAC, endoscopic procedure and important notes of study subjects

Age/Sex	Site	Endoscopic Surgical Procedure	Important Notes
9 y/M	Left temporal	CC (basal cistern)	--
12 Mon/M	Right frontoparieto-temporal	CV (frontal horn)	Simultaneous left frontal hemorrhage
9 y/M	Right frontal with extradural cyst	CV (Frontal horn)	Symptoms were gone but very minimal radiological reduction of IAC
4 Mon/F	Posterior fossa	ETV (at 4 months); CV (Through posterior parietal trans-trigonal, 3 years old)	Cyst grew with age of the patient
50 y/F	Right posterior parietal	CV (lateral ventricle)	Preoperative –total blindness; Visual recovery near to normal) after operation
45 y/F	Left parieto-occipital	First: Burr hole evacuation of CSDH, later: CV (lateral ventricle)	There was simultaneous Right frontoparietal CSDH
14 y/M	Right frontotemporal	CV (frontal horn)	--
7 Mon/M	Right frontoparietal	CV (frontal horn)	--
6 Mon/M	Left frontoparietal	CV (lateral ventricle)	Bilateral occipital encephalomalacia
10 y/F	Right occipital	Through occipital burr hole-CV (occipital horn)+ through Kocher's point burr hole-ETV	HCP resolved
47 y/F	Third ventricular cyst	CV+ETV (double fenestration)	HCP resolved. There was cirrhosis of liver.
06 Mon/F	Right frontal	CV (frontal horn)	Unilateral HCP (mono lateral ventricular HCP)
31 y/F	Right paramedian (median longitudinal fissure), parietal	Endoscopic microsurgical transcalsal CV (lateral ventricle)	Preoperative hemiplegia-recovered post operatively
13 y/M	Supracerebellar-pinealo-3rd ventricular	ETV+CV(trans third ventricular)	--
12 Mon/F	Whole post fossa + occipital	ETV- through Kocher's point burr hole + CV (lateral ventricle)-through a more anterior burr hole	Preoperative HCP resolved
7 Mon/F	Pineal huge HCP	ETV + CV (Third ventricle)	HCP. Two frontal burr hole
3 y/M	Right frontoparietal	CC (basal cistern)	--
7 y/F	Third ventricular	CV+ETV(double fenestration)	--
17 y/F	Right sided cerebellopontine angle	Endoscopic microsurgical -CC (Prepontine cistern, double fenestration)	--
9 y/M	Suprasellar arachnoid cyst	CV+ETV (Double fenestration)-at 9 years old. Re-ETV at 16 years of age	Stoma block seven year after operation (re-appearance of HCP)
29 y/F	Left parietal	Transparietal lobule- Endoscopic microsurgical (with Neuronavigation)CV (lateral ventricle)	--
23 y/M	Right temporal	Endoscopic microsurgical transtemporal CV(temporal horn)+CC (basal cistern)	Preoperative seizure was gone
55 y/F	Right frontoparietotemporal	Endoscopic microsurgical frontal transcortical -CV (frontal horn)	--
17 y/M	Suprasellar cyst	ETV+CV (Double fenestration)	--
3/M	Suprasellar IAC	ETV+CV (Double fenestration)	--
1/M	Left frontal IAC	CV (frontal horn)	--
18 Mon/M	Right frontoparietal	CV (frontal horn)	--

Abbreviations: y: year; M: Male; F: Female; IAC: Intracranial Arachnoid Cyst; CV: Cysto-Ventriculostomy; CC: Cysto-Cisternostomy; ETV: Endoscopic Third Ventriculostomy; HCP: Hydrocephalus; CSDH: Chronic Subdural Hematoma

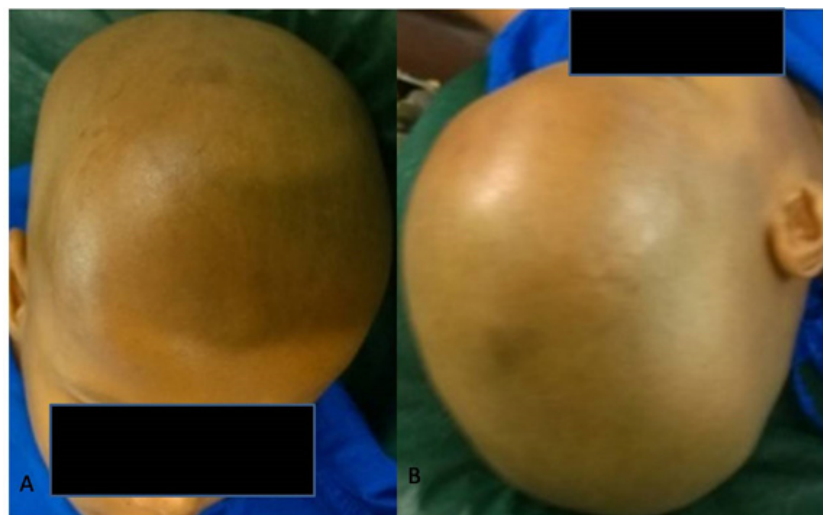


Figure 2. Asymmetry in the frontal region between right and left side due to underlying arachnoid cyst

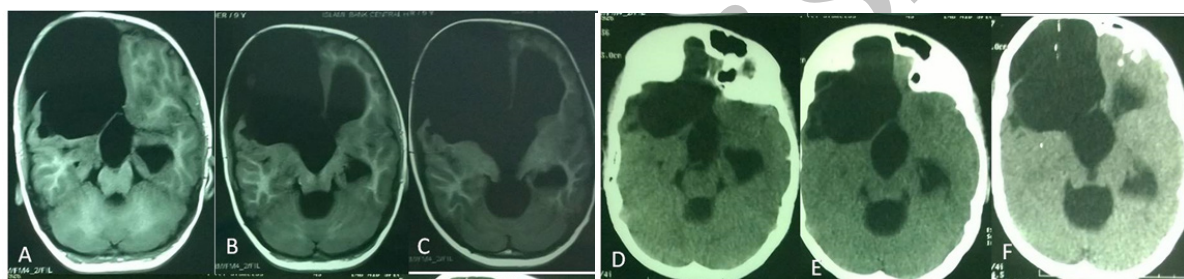


Figure 3. Preoperative and post operative neuro-images of the patient

A, B, and C: Preoperative MRI of brain axial sections in T1W showing both extra and intradural right frontal IAC (Figure 2); D, E, and F: Post CV CT scan of head axial images showing very minimum reduction of size of IAC (though symptoms were gone).

Hydrocephalus (HCP) (including one mono-ventricular HCP) (Figure 3, 4, and 5). Clinical features are shown in the Table 1. Two patients had chronic headache with sudden exaggeration where imaging showed Intracerebral Hemorrhage (ICH) in one case (Figure 6) and chronic subdural hematoma in another case.

Imaging findings

Only brain CT scan had been done in 6 cases and only brain MRI in 14 cases whereas both CT and MRI had been done in 7 cases. On neuro-imaging, mass effect of IAC was seen in all the cases in the form of sulcal effacement, neighboring cortex depression, ventricular

Table 3. Mortality, major morbidity, recurrence/reoperation with follow up

Cases (n=27)	No.	%	Follow Up: 89-09 Mon; Average: 18.5 Mon
			Comment
Perioperative mortality	00	00	One patient died 4 years after operation due to cirrhosis of liver
Postoperative new neurodeficit	00	00	
Recurrence of symptom/s	01	3.7	Due to stoma obstruction (after 7 years)
Re-operation	01	3.7	Re-ETV

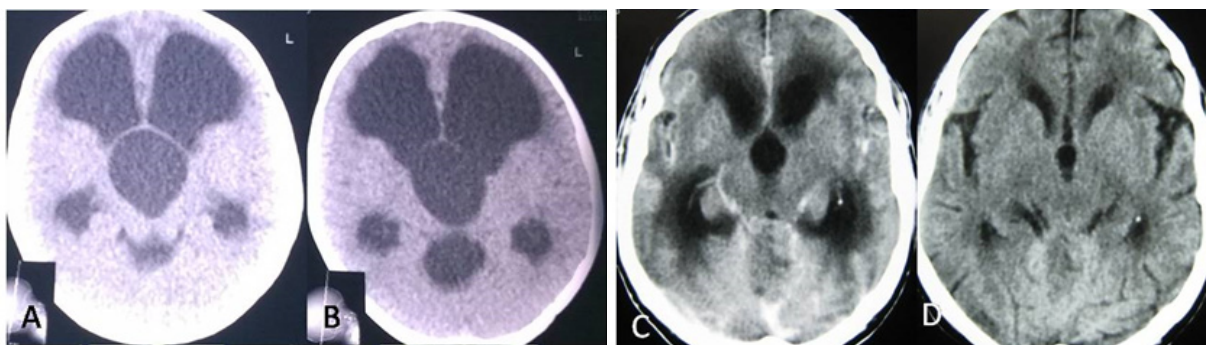


Figure 4. Pre and post operative CT scan of head

A, B: Preoperative CT scan of brain at the age of 9 years showing suprasellar/third ventricular IAC; C: CT scan of brain at the age of 16 showing development of triventriculomegaly due to stoma block; D: Postoperative CT scan of head after ETV.

effacement or enlargement, and midline shift. Hypoplasia of the adjacent brain parenchyma was also found in most of the cases, especially temporal lobe hypoplasia in temporal/sylvian IAC. Thirteen were in the right side, 5 in the left side, and 9 in the midline.

Age, sex, site, operative procedures and important notes are shown in [Table 2](#) ([Figures 1-11](#)). Mortality, major morbidity, recurrence/reoperation with follow up are presented in [Table 3](#). Flexible endoscope was used in three cases whereas rigid endoscopy was used in 21 cases. Flexible endoscope was replaced by rigid

endoscope in later part of surgery in 3 cases. It seemed that working with rigid endoscope was faster let alone its better illumination and vision. Pure endoscopy was used in 23 cases while endoscopic microsurgical (rigid endoscope+microsurgical instruments) techniques were used in 4 cases. In one case, neuronavigation assistance was taken during microsurgical transcortical cysto-ventriculostomy.

Cysto-Cisternostomy (CC) was done only in three cases, Cysto-Ventriculostomy (CV) ([Figures 6, 7, and 8](#)) was done in 13 cases, CC+CV was done in 1 case and CV+ETV (endo-

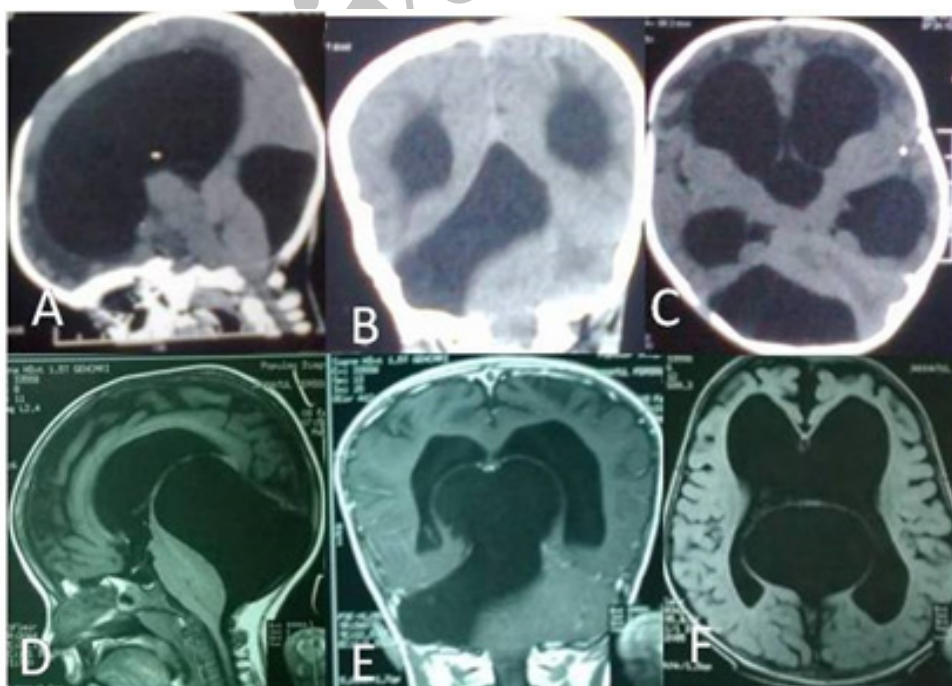


Figure 5. CT scan of head

A: Sagittal; B: Coronal; C: Axial image before ETV at the age of three months, showing posterior fossa IAC with triventriculomegaly. Post ETV MRI of brain at the age of three, D: T1W sagittal; E: Contrast coronal; and F: T1W axial images showing growth of IAC and extended into lateral ventricle (for which translateral ventricular CV needed).

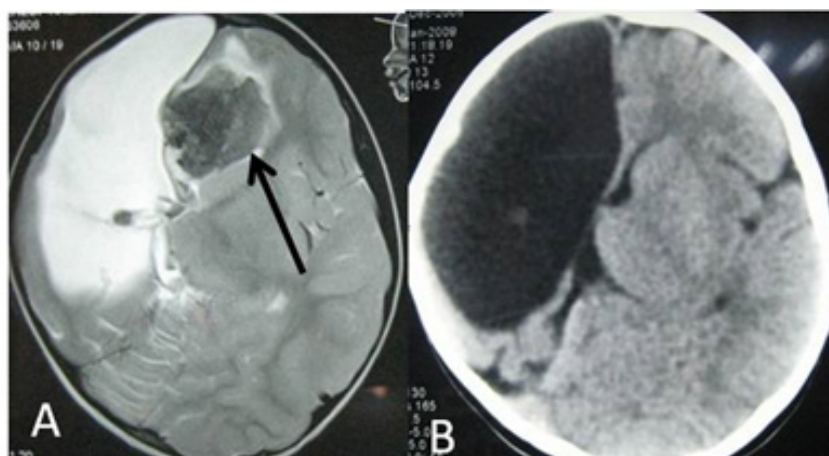


Figure 6. Pre and post operative neuro-images

A: MRI of brain T2W axial image showing right sided IAC with left frontal intracerebral hemorrhage; B: Postoperative CT scan of head showing cyst as like that of preoperative image (though symptoms were gone).

scopic third ventriculostomy) (Figure 5), including 'double fenestration' (Figure 9) was done in 10 cases, where HCP was present. Hydrocephalus in CP angle IAC resolved after CC. Mono-ventricular HCP was resolved with the treatment of IAC i.e. cysto-ventriculostomy. In the case of IAC with Intracerebral Hemorrhage (ICH), only CV was done and ICH was resolved spontaneously (Figure 6). Chronic subdural hematoma was treated earlier before CV in the case of IAC with chronic subdural hematoma.

Single burr hole was done in 20 cases, two burr holes were done in 3 cases and small craniotomy (2x2 cm)

done in four cases of endoscopic microsurgical procedure (Figures 10 and 11). In one case, ETV was done at the age of 4 months and cysto-ventriculostomy was done at the age of 3 years where cyst enlarged and insinuated into lateral ventricle (trigone and body) (Figure 5). Thus, posterior parietal transcortical transventricular CV was done. This patient also had corpus callosal agenesis.

Preoperative bleeding occurred in three cases that was controlled with irrigation and endoscope tip pressure/ inflated Fogarty catheter balloon. In one case, partial injury of fornix occurred near foramina of Monro with-

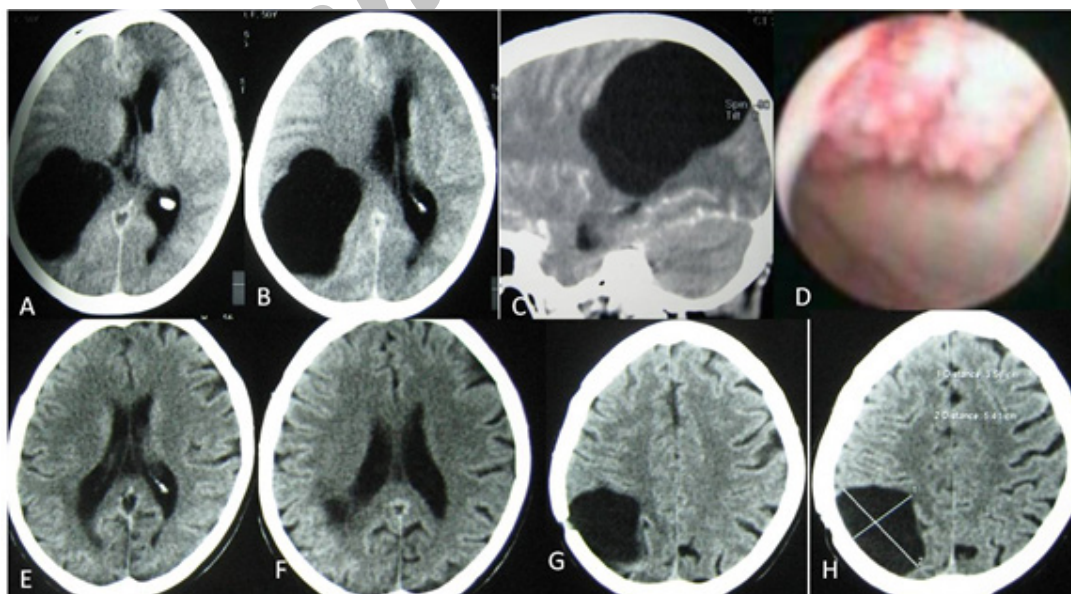


Figure 7. Preoperative CT scan of head

A and B: Axial section; C: Sagittal section showing right parieto-occipital IAC with mass effect; D: Preoperative picture of ventricular choroid plexus after CV; E, F, G, and H: Postoperative CT scan of head axial section after CV showing reduced size IAC without any mass effect.

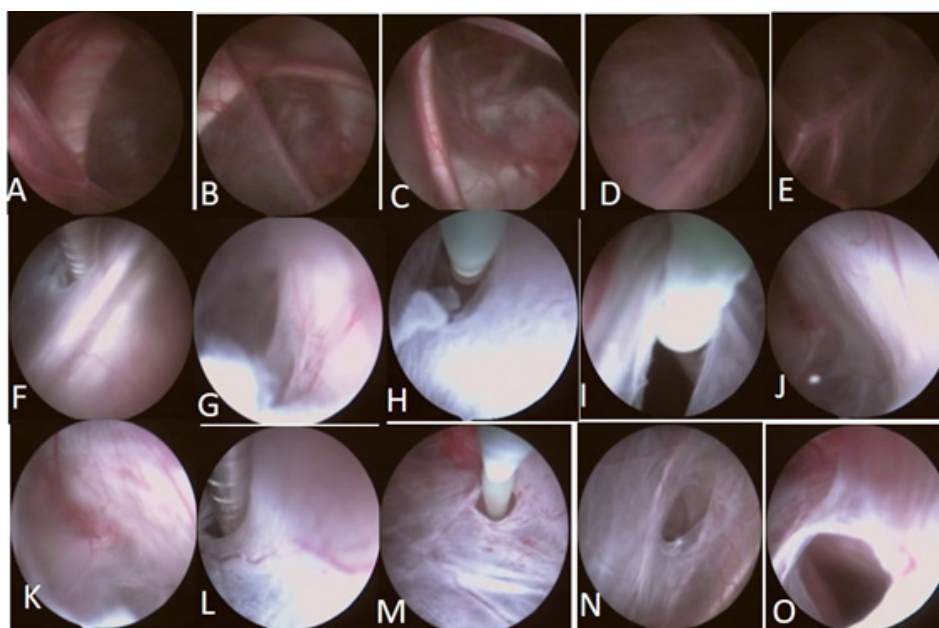


Figure 8. Preoperative sequential picture of different stages of endoscopic 'double fenestration' of a suprasellar/third ventricular IAC

A, B, C, D, E, F, G, H, and I: First wall fenestration; J, K, L, M, N, and O: Second wall fenestration.

out any postoperative complication. Histopathology confirmed the diagnosis of 'arachnoid cyst', in all cases. Most of the patients were discharged within three days after operation (range 2 to 7 days). Preoperative hospital stays were between 1 to 14 days.

Early postoperative convulsions occurred in two cases which were managed with injectable antiepileptic. Post-

operative fever (37.5°C - 38.3°C) occurred in 4 cases. Minor wound infection (i.e. stitch infection) occurred in two cases.

A patient with preoperative hemiplegia (recovered almost completely six weeks after operation (Figures 9, 10, and 11).

In all cases of IAC, size of the cyst decreased (significant to minimal, seen in follow up images in compari-

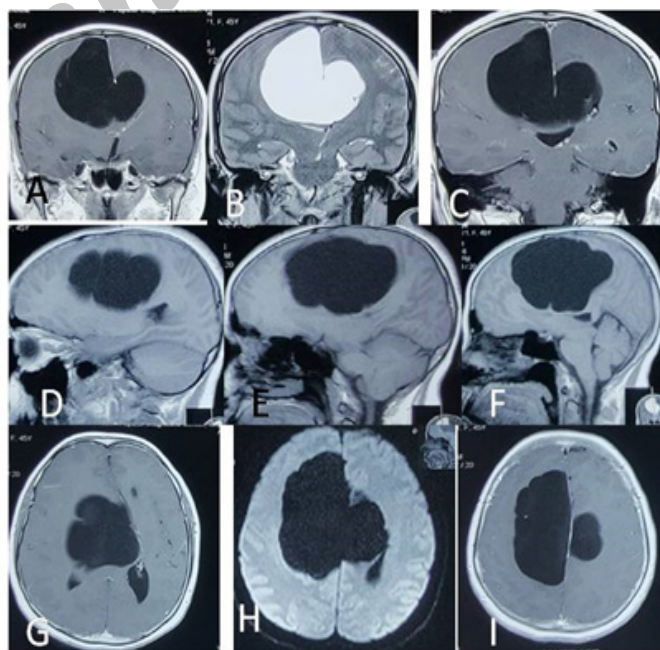


Figure 9. Preoperative MRI images of brain of frontoparietal interhemispheric IAC with mass effects

A and C: Contrast coronal; B: T2W coronal images. D, E, and F: T1W sagittal images; G and I: Contrast axial and H: DW image.

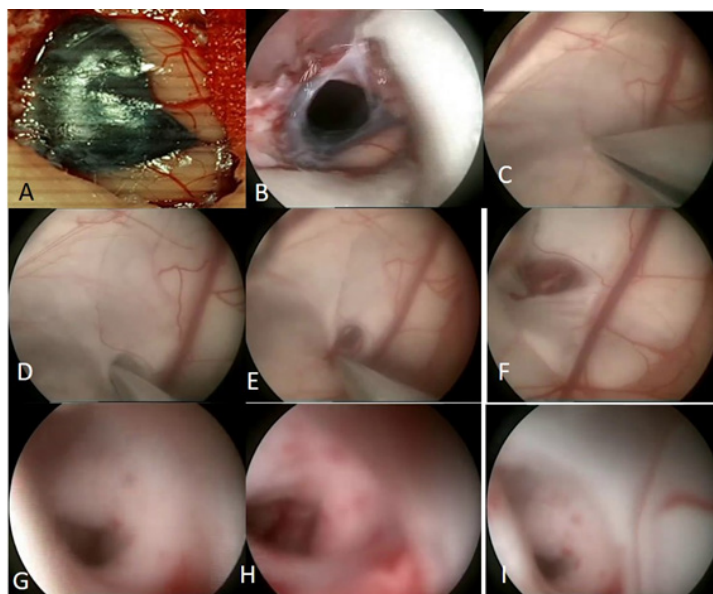


Figure 10. Preoperative sequential images in the way of endoscopic microsurgical transcallosal CV of the interhemispheric IAC (Figure 11)

A: After durotomy; B: Just before entering into cyst; C: Just before callosotomy; D, E, F, G, H, and I: Different steps in the way of transcallosal CV.

son to the preoperative images). First follow up image was done before hospital discharge and second follow up image was taken 8-12 weeks after operation. Even if size reduction was minimal, patient's symptoms improved significantly within 1 day to 12 weeks (average: 2 weeks). No IAC increased in size after endoscopic proce-

dures. Preoperatively, two patients had visual problems; one who was preoperatively completely blind regained vision near to normal within 3 months after the operation (Figure 7) and the other one remained unchanged.

There was no recurrence of symptoms in the follow up period (average 18.5 months). There was no postopera-

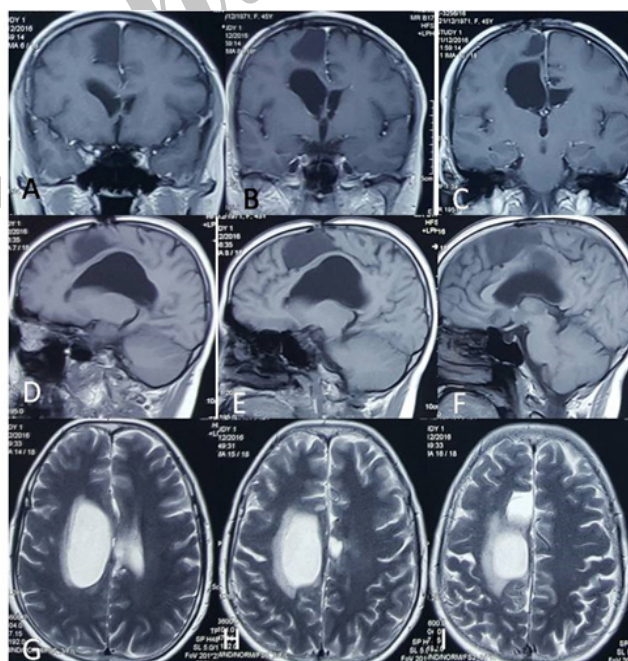


Figure 11. Postoperative MRI of brain

A, B, and C: Contrast coronal; D, E, and F: T1W sagittal; G, H, and I: T2W axial images showing much reduction in size of IAC with no mass effect.



tive mortality or major morbidity related to surgery. One patient experienced symptoms of increased intracranial pressure 7 years after operation due to obliteration of third ventriculostomy and responded well after repeating ETV (Figure 4). One patient with concurrent cirrhosis of liver became symptoms free (due to IAC) postoperatively but died of liver failure 4 year after operation. Rest of the patients were doing well till last follow up.

4. Discussion

IACs are developmental abnormalities of the arachnoid membrane that gets duplicated or split. This occurs during the early embryonic period [2, 9, 10]. Arachnoid cysts are also associated with other central nervous system anomalies such as partial or complete agenesis of lobes [11]. CSF dynamics can result in an increase in the size of some cysts or rupture leading to elevated Intracranial Pressure (ICP). The underlying mechanisms may be active secretions from the cyst wall, a valve like mechanism, or obstructed outflow. Others include aberrant fluid dynamics and osmotic changes along the cyst wall [2, 9, 12]. This may cause a persistent and continual mass pressure that can affect the normal development and function of the surrounding brain [13-16]. The prevalence of IAC is 2.6% in children and 1.4% in adults [6, 7] and is a frequent incidental finding [6, 17].

IAC can be supratentorial or infratentorial. In supratentorial region, IAC can be in sylvian fissure, cerebral convexity, sellar or suprasellar, interhemispheric or quadrigeminal. In infratentorial region, IAC can be found in posterior midline, clival, cerebellopontine angle, vermis or in cistern magna [18]. Site distribution of IACs of our series was similar but we did not find any clival arachnoid cyst. Majority of IACs are asymptomatic [18]. However, IAC can present with symptoms depending on the location of cyst and age of the patient. Patients can present with headache, seizures, gait disturbances, cognitive decline, focal neurologic deficits, cranial nerve palsy, dimness of vision, and increase in head circumference. Young patients are prone to cyst enlargement so they need surgical interventions as early as possible. Suprasellar cysts usually present with typical bobble-head doll syndrome and endocrine or visual abnormalities.

Hydrocephalus is a common manifestation in posterior fossa cysts and periventricular cysts. In neonates and younger children, presenting symptoms are usually due to elevated ICP. Neurosurgeons agree that symptomatic IACs patients who present with symptoms of intracranial hypertension, intractable seizures, and focal

neurologic deficits warrant surgical management [19-22]. Clinical features of IAC in our study were (in order of frequency) headache, hydrocephalus, gait disturbance, head asymmetry, visual disturbance, epilepsy and limb weakness. However, the most effective surgical management still remains controversial [23, 24]. Surgical options available are simple burr hole and cyst aspiration, open craniotomy for cyst removal or fenestration into adjacent arachnoid spaces, shunting or stenting of cyst contents into ventricle, endoscopic fenestration or cysto-peritoneal shunt operation [25]. Age is not a limiting factor for these surgical options [26].

Endoscopic decompression of the cyst is minimally invasive, safe, and easy, less time consuming, and a lower incidence of postoperative complications. Other endoscopic procedures include endoscopic cysto-cisternostomy, cysto-ventriculostomy, or partial cyst wall excision [3]. The choice of surgery depends on the patient's age, the distance between the lesion and the neighboring ventricle or cistern, presence of hydrocephalus, mass effect caused by cyst, and relation with surrounding structures. Among surgical options, primary endoscopic fenestration appears to be an ideal procedure [27]. We used only endoscopic cysto-ventriculostomy and cysto-cisternostomy (where nearby ventricle was not available but cistern was available). Double fenestration was used in third/suprasellar arachnoid cysts. Where there was a thick layer of parenchyma between cyst and ventricle microsurgical assisted endoscopic cysto-ventriculostomy (rigid endoscope+ microsurgical instruments) was done and in such cases neuronavigation can be helpful for safety and accuracy.

Microsurgical craniotomy is some time preferred for patients with arachnoid cysts located in the cerebral convexity and intracerebral. Local skull cranioplasty can be done in patients whose preoperative diagnosis showed features of cystic tumor or cyst-related epilepsy. Total resection or partial resection of the cyst wall can be for full fenestration. The combined use of microsurgical fenestration and cysto-ventriculostomy or cysto-cisternostomy can be performed simultaneously. Microsurgical craniotomy provides a full space for the total resection of the arachnoid cyst with Electrocorticography (ECoG) monitoring to record epileptic form discharges and thus localizing epileptogenic zone [28]. This approach also allows the surgeon to perform other procedures like focus excision, cortical thermo-coagulation, or local skull cranioplasty. Microsurgical craniotomy was more invasive than endoscopy, but it is argued that the microsurgical technique can obtain greater control of hemostasis because of the ability to use bipolar

forceps. 19 A full space ensures the ability to perform another operation for cyst-related diseases, particularly in cyst-related epilepsy.

Extensive and mature application of endoscopy can replace microsurgical craniotomy gradually; however, the latter technique is more efficient for cortical arachnoid cysts, cyst-related epilepsy, or cysts with preoperative diagnosis for the possibility of a cystic tumor [23, 28]. Endoscopy is now a popular method for surgical treatment of arachnoid cysts. This treatment involves the use of a high-definition and stereo-vision system to visualize the arachnoid cyst and its neighboring structures. In addition, the technique provides an easy and minimally invasive method for cysto-ventriculostomy or cysto-cisternostomy. Therefore, endoscopy is a safe and effective therapeutic modality for IAC [29-31].

Cystoperitoneal shunting is effective for large cysts, particularly by using the low pressure shunt. However, recurrence of the cyst and shunt related complications are the problems, thus cystoperitoneal shunting should not be the first choice nowadays. Surgical treatment of arachnoid cysts may occasionally result in complications, including pseudomeningocele and CSF leak [31] wound related complications, 31-33 infection, 31 subdural hygroma. [31, 33] subdural hematoma [32, 33] seizure, 31 redo surgery [31, 32] and the risk of shunt dependency and its over drainage [34]. In patients with symptomatic arachnoid cysts, treatment may lead to lasting relief of focal neurological deficits [35, 36].

Seizures and headaches, however, often persist despite adequate surgical treatment of the cyst [31]. Most arachnoid cysts do not resolve completely as seen in our case series. In this series, postoperative imaging showed a significant decrease in cyst size in 7 patients and only a slight decrease in cyst size with a resolution of symptoms in others. Preoperative symptoms and signs were improved postoperatively like other endoscopic series in the literature. There was no mortality or major complication in our study that concur results of other reported endoscopic series in the literature [29-31].

The reason for noncollapsibility of these cysts is that they are developmental cysts and associated with agenesis of lobes [2, 9, 12]. Haemorrhage into the subdural space or into the arachnoid cyst has been reported in patients with arachnoid cysts [37-39]. It is a rare event and not even a single patient in the natural history group experienced a hemorrhage. Hemorrhages associated with arachnoid cysts that have been reported in the literature are generally related to good outcomes [39]

and surgery may not eliminate the risk of future hemorrhage in these patients [18, 40]. Thus, prophylactic surgery is not recommended in asymptomatic IAC.

Our study had some limitations. Follow up period was too short to see the recurrence of IAC. As the number of operated cases are small, adult and pediatric patients are presented simultaneously. Therefore one can argue that an arachnoid cyst in a pediatric patient is a very different disease than a symptomatic arachnoid cyst in an adult although they may radiographically and histologically look similar. Finally, rigid and flexible endoscopic procedures and endoscopic microsurgical (rigid endoscope + microsurgical instruments) procedures are presented without differentiation.

5. Conclusion

In symptomatic IAC, endoscopic procedures (in different forms) are attractive surgical options. Almost all types of symptomatic IAC can safely and effectively be managed by endoscopic procedures. Thus, large craniotomy or various shunt procedures in IAC can effectively and efficiently be avoided.

Ethical Considerations

Compliance with ethical guidelines

There is no ethical principle to be considered doing this research.

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Authors contributions

All authors have read and approved the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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