PROSPECTIVE OBSERVATIONAL STUDY OF OUTCOMES OF DIFFERENT TRANSCRANIAL APPROACHES FOR CRANIOPHARYNGIOMAS

Submitted for M.Ch Neurosurgery

By

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DECLARATION

This thesis titled – Prospective Observational Study of outcomes of Different Transcranial approaches for Craniopharyngiomas is a consolidated report based on a bonafide study of the period from December 2017 to July 2019, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of MCh Neurosurgery examination.

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CERTIFICATE

This is to certify that the thesis entitled – **Prospective Observational Study of outcomes of Different Transcranial approaches for Craniopharyngiomas** is a bonafide work of Dr. Jaypalsinh Gohil and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

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Dr. Jaypalsinh Gohil

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INTRODUCTION :

Craniopharyngioma:

"One would expect these congenital epithelial tumors to be capable of enucleation like Dermoid cysts elsewhere in the body, but they so definitely adhere to the adjacent structures neighboring on their place of origin, it is rarely possible to shell them out of their bed without the production of serious secondary symptoms. To be sure, one may occasionally succeed in stripping out a thin-walled cyst, and examples of this have been reported, but when the tumor is partly solidified, and calcareous, sad experience warns the surgeon to leave it pretty much alone." Harvey Cushing, 1932. (1)

"Though this tumor is still an ominous disease, it seems fair to say, that the outlook has improved considerably." (2)

Craniopharyngiomas are rare CNS tumors defined by WHO as benign, partly cystic epithelial tumor of the sellar region presumably derived from Rathke's pouch epithelium. While it is benign in nature, the adhesion to surrounding structures may result in damage to sellar and parasellar tissues during surgery and hence it is called "Benign Tumor in a malignant location." (3)

However due to introduction of hormonal therapy has allowed optimal correction endocrinal deficiency, and improvement in radiation and microsurgical techniques have improved survival enormously, it is the quality of survival that has become real challenges.

The results of the published studies of neuropsychological outcome in children are often conflicting and controversial. However surgical approaches of craniopharyngioma need to be addressed with regards to neuropsychological outcome. This study serves the above mentioned purpose.

AIM AND OBJECTIVES

To study different outcome especially neuropsychological outcome of different transcranial approaches for craniopharyngiomas.

REVIEW OF LITERATURE

Epidemiology:

Incidence: The data from 15 population-based craniopharyngioma studies, which included over 1000 cases, suggested the estimated incidence to be 1.34 patient per 1 million people. (4)

In the US during 2005-2009, 0.9% of new cases were reported in the population, with a higher percentage among people in the age group of 0 to 14 years, that is 4.1%. (5)

Age predilection: Craniopharyngiomas show a bimodal age distribution with a peak incidence at ages 5-14 years and then again in the elderly population at around 65 years of age. (6) However, cases have also been reported in, as young as, the prenatal period, and as old as, in the 9th decade of life (7,8).

Geographic location : Highest incidence has been reported in African and Asian population. (6) Nigerian study reported 38% intracranial Tumor harbored by the pediatric population was craniopharyngioma during 1985. The above statistics may be biased because of poor diagnostic modalities. (9,10). A Japanese study, Mori and Kuriska 1986 reported 5.8% of craniopharyngioma with 12.5% in children. (11). Cheng et al in 2012 reported a craniopharyngioma incidence of 6.5% in China. (5)

Environmental and familial factors: No environmental risk factors have been found to be associated with craniopharyngioma. There is no clear familial tendency associated with it. However, 3 case reports showed the occurrence of craniopharyngioma in siblings and one in the first cousin. This may suggest an autosomal recessive trait associated with tumor occurrence. But overall craniopharyngioma is a rare and spontaneous occurrence. (6,12,13)

Pathophysiology:

Histologically craniopharyngioma can be divided into two class-adamantinomatous which occupy major component and papillary. Both are derived from Rathke's pouch epithelium.

Adamantinomatous craniopharyngioma occurs predominantly in the pediatric population. Grossly, it shows calcification and is solid-cystic in nature. It contains a cholesterol-rich motor oil like fluid which is corrosive in nature if it comes in contact with the normal parenchyma. Microscopically, solid part shows a palisading arrangement of columnar cell layers that encase loose stellate epithelium and desquamated epithelial cells, also called wet keratin. Rosenthal fibers are also seen at the interface of the tumor with the normal parenchyma, which shows gliosis. (14)

Adamantinomatous craniopharyngioma is believed to arise from tooth forming epithelium stomodeum, which somehow undergoes neoplastic changes. These cells become trapped in the craniopharyngeal duct. This theory is called "embryogenic theory of craniopharyngioma development". This embryogenic basis may explain the reason for Adamantinomatous craniopharyngioma being common in the pediatric population and also for the presence of calcifications in it. (14,15)

Papillary craniopharyngioma is primarily seen in the adult population. The tumor is more solid and uniform in nature with a fibrovascular core. It also contains wet keratin as described above but squamous epithelial cells are well differentiated. This variant typically lacks calcification and contains less cystic intratumoral fluid. (16)

The embryological basis of the origin of papillary tumor is explained by metaplastic theory. Pars Tuberalis contains adenohypophyseal cells which undergo metaplasia and form papillary craniopharyngioma. In short, Adamantinomatous craniopharyngioma originated from neoplastic changes in the epithelial cell in craniopharyngeal duct and Papillary craniopharyngioma arise from cells in craniopharyngeal duct undergoing metaplastic changes. Therefore, it is usually rare in young patients as it will take time to undergo metaplasia. (14,15,17)

Recently, the origin of craniopharyngioma is believed to be a combination of the above two hypotheses. Szeifert et. al., reported 131 craniopharyngioma patients in which 15% contained both squamous (Papillary) and Adamantinomatous features (18).

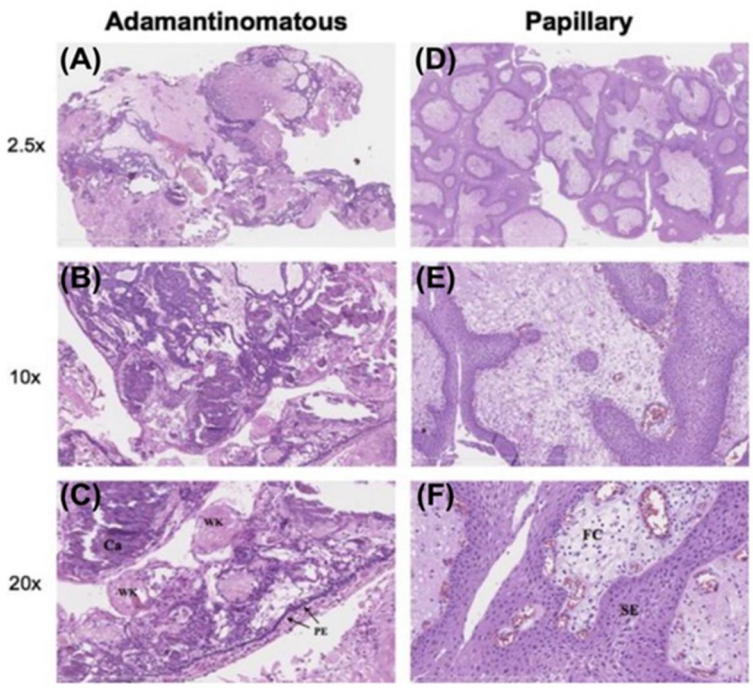


Figure 1: Histological sections of craniopharyngioma. A-C, Adamantinomatous type consisting of epithelial lobules with loose stroma, wet keratin (WK), calcifications (Ca) and peripheral palisading epithelium (PE). D-F, Papillary type consisting of sheets of well-differentiated non-keratinizing squamous epithelium (SE) in a papillary configuration, with a broad fibrovascular core (FC). Magnification is indicated on the left. (Courtesy of Jiang Qian, MD, PhD; Albany Medical Center Department of Pathology

A historical aspect:

Before 1900: In a Dutch village of Voorsanti in 1590, an 18-year-old girl had died. She had history of polyuria and she had become blind before her death. Her father asked the anatomist Pieter Pauw (1564-1617) at the University of Leyden to perform private autopsy – a request not common in society during that era (19). Until world war I diabetes insipidus was believed to be of renal origin. Thus, it is supposedly the first example of craniopharyngioma being reported indirectly in the literature. Though in that era, it was difficult to prove the diagnosis.

Bonet of Geneva in 1679 described a child with a cystic tumor which seemed to originate from infundibulum and contained 1000ml of fluid within, as reported by Zenker. (20) He also described another case with large cyst derived from the pituitary.

Boyce and Beadles are the first to publish a systematic case series of pituitary tumor including sellar tumor which may include craniopharyngioma.

First detailed description of histopathology of the tumor was given by Mott and Barratt. They reported 3 cases with ventricular extension and one of them was large multiloculated cystic tumor with hydrocephalus and displacement of the optic chiasma. (21)

Later Saxer described a 46-year-old male with a large infundibular tumor but normal pituitary gland. From his description, the tumor seems to be papillary craniopharyngioma. (22)

After 1900: In 1904, Jocasta Erdheim (1874-1937), a pathologist at General Hospital, Vienna provided the detailed knowledge about craniopharyngioma by various publications. He performed an autopsy on an elderly woman who died of Graves' disease and cardiac insufficiency. As he was interested in the fat cell in pituitary he performed autopsy and pituitary was closely observed. He had found a small cyst on anterior pituitary lined with cuboidal/ squamous cell. It was different from Rathke's cyst. He has noted this thing had never been reported before so decided to explore this pathology and study on it. (23)

Erdheim was aware of the origin of pituitary that anterior lobe arises from craniopharyngeal duct, the cranial part of ectodermal epithelium from primitive mouth called stomatodeum. He also contributed similar origin in the thyroglossal duct. Hence, he called it hypophysenganggeschwulste (Tumor of the hypoglossal duct). (23)

For many years, Erdheim's presumption of craniopharyngioma origin was accepted. In 1932, Harvey Cushing used the term Craniopharyngioma. However, he was not the first to use this term and he stated that the "cumbersome" word encompassed" the kaleidoscopic tumors, solid and cystic in nature, which take their origin from epithelial rests ascribable to an imperfect closure of the hypophysial or craniopharyngeal duct'. (1)

Treatment:

A.E Halstead performed the first known operation for craniopharyngioma on a 39-year old patient in Chicago during 1909, who presented with headache and progressive bitemporal hemianopsia. He used transsphenoidal approach and blue colored mass was excised following which the patient was improved. Pathological description of the tumor led the surgical team to conclude that this was an "epithelial tumor developing in Sella turcica from the fragment of undifferentiated epithelium developing from craniopharyngeal duct"- an Erdheim tumor. (24)

Cushing had also been among the first to operate Craniopharyngioma by trans sphenoidal route. He evacuated the cyst containing motor oil fluid, rich in cholesterol crystals. He also reported Cerebro-spinal fluid leak with meningitis in that patient, from which the patient recovered. Practically, a normal vision was regained and was preserved until 10 years. He operated again for the recurrence in that patient.(1)

Thus, the outcome in the patient undergoing surgery was gratifying. However, it soon became clear that the long-term outcome was disappointing. In Cushing series, the mortality after surgery was 15%, much higher than pituitary adenoma.

The first operation was performed via trans sphenoidal route, but craniotomy, soon, became the procedure of choice. Halstead chose to operate by transsphenoidal route due to his belief that the patient had pituitary adenoma. While Cushing approached such lesions via transsphenoidal route initially, he preferred transcranial route in his subsequent cases. He concluded that the morbidity of the trans nasal technique was high. So trans-cranial approach became more popular including supraorbital pterional, trans-petrosal, trans-tentorial, and sub frontal approaches. (25)

A renewed interest in trans sphenoidal surgery began in 1960 led by Jules Hardey and Guiot with their utilization of video fluoroscopy. The endonasal approach for craniopharyngioma was further supported by a case series by Edward laws in 1980. Gardener described expanded endonasal endoscopic approach, in view of the wide corridor and better resection. (26,27)

The reported operative mortality rate was very high during 1927-1949, almost reaching as high as 41% and 22% mortality was reported due to the recurrence of the

tumor. Other case series reported 33% during 1936-1947, 29% during 1929-1945. (28–(2)30)

A major reason for the high mortality was unavailability of steroids and its significance was not given due importance. Once corticosteroid was available in 1950s, the operative mortality significantly reduced. However, morbidity remained high. In larger series after the 1950, mortality was reported to be 10-40%. A Swedish neurosurgeon, Olivecrona, operated 107 craniopharyngioma cases and reported useful survival accomplished in only one-third of the patients. (31,32) While complete surgical excision may provide a cure, it may also be accompanied by significant morbidity. The surgical paradigm has therefore shifted so that, gross total resection was the goal only when obtainable, and adjuvant therapies have started to play a larger role in the treatment.

The first report regarding the use of radiation in the management of craniopharyngioma was published in 1930 by Carpenter. (33,34) Now, conventional radiotherapy has clearly shown its effectiveness in controlling tumor growth, when given either immediately after subtotal resection or as salvage therapy. Minniti et al noted that craniopharyngioma recurrence after subtotal resection may approach up to 85%. However, several large series documented local control rate of about 77-89% at 10 years and 20 years local control rate of 54-79%, when radiotherapy is administered after surgery. (35)

Regarding Stereotactic Radiosurgery, Gopalan et al assessed the outcome after radiosurgery between 1995-2005 and concluded that radiotherapy is valuable in controlling tumor growth. (37) Fractionated stereotactic radiotherapy and stereotactic radiosurgery have the potential benefits and lesser side effects, but further studies require to confirm. Intracavitary irradiation can also be utilized for predominantly cystic craniopharyngioma. (36)

Chemotherapy has also demonstrated promise as another adjunctive treatment for craniopharyngioma, however, overall application is limited. (38)

Concurrent with progress in imaging and surgical techniques, medical substitution treatment has also improved including stunted growth which was most

common complication previously. Although this tumor is still an ominous disease, it seems fair to say that the outlook has improved considerably.

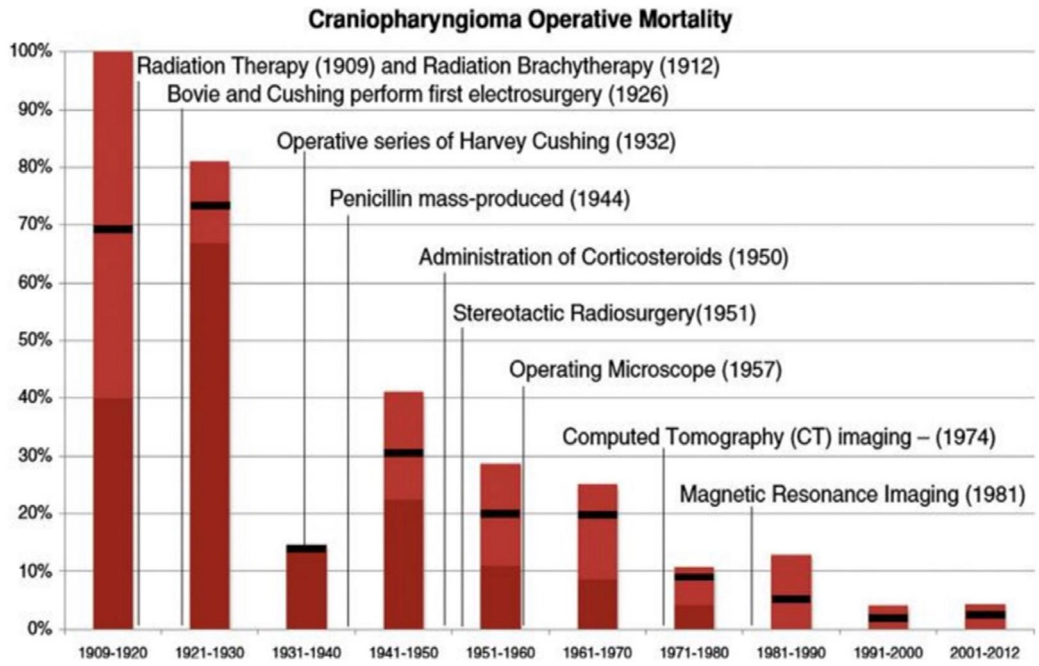


Figure 2: perioperative mortality based on selected series of craniopharyngioma patients (n>10), published within the date range provided.(2)

Presentation and modern disease course:

Craniopharyngioma commonly presents with the mass effect on adjacent structures and local invasion. This causes distortion of sellar, parasellar space, chiasma, pituitary apparatus, hypothalamus, and ventricular system. So, most common presentations are vision changes, endocrine changes and symptoms related to increased intracranial pressure. (40)

Karavitaki et al reported that adults presented commonly with visual disturbance, but children commonly presented with increased intracranial pressure, endocrine dysfunction and headache. Headache from raised intracranial pressure is the most common complaint, occurring 60% to 75% of patients. Visual symptoms are noted in approximately half of the children. Hypothalamic and endocrine dysfunction such as short stature, delayed puberty, weight gain and diabetes insipidus are present in 20% to 50% of children at diagnosis. (17) (4)

Overall, those patients with endocrinopathies seek medical attention after a long duration of symptoms. In a review of 122 cases, the median time between initial symptoms and diagnosis was 27 months, with a maximum of 15 years. (41)

Evaluation and Management:

Evaluation of craniopharyngioma patients is similar to the workup of other sellar mass. It includes endocrine evaluation (Pituitary hormones), neuro-ophthalmological evaluation (visual acuity, field testing by perimetry) and imaging study i.e., MRI with contrast (with both coronal and sagittal view reconstruction required). Around 80% of children have demonstrated abnormal visual acuity or field on preoperative testing. The specific visual deficit depends on the direction of growth of the tumor and its compression of various portion of optic nerves. Various level optic nerve compression results in loss of visual acuity and chiasmatic compression results in bitemporal hemianopsia. Less than 30% of children are endocrinologically normal at diagnosis. Growth hormone deficiency is the most common finding, present up to 75% of children. Gonadotropin and thyroid or adrenal dysfunction is seen in approximately one-third of children.

Tumor classification:(42)

Hoffman et. al., classified craniopharyngioma in intrasellar, prechiasmatic, and retrochiasmatic.

Samii divided craniopharyngioma depending on ventricular extension:

I-purely intrasellar

II-cistern =/- intrasellar component

III-lower half of third ventricle.

IV-upper half of third ventricle.

V-extend in to lateral ventricle.

Kassam et al proposed classification depending on relation with stalk-

I- Pre-stalk

II- trans stalk.

III- Retro stalk

IV- Metastalk involving basal ganglia even middle cranial fossa.

V- Ectopic type located in paranasal area, third ventricle, forth ventricle.

Yasergil et al in 1990 classified craniopharyngioma in relation with diaphragm

Purely intrasellar-infradiaphragmatic

Intra- and suprasellar, infra and supradiaphragmatic

Supradiaphragmatic parachiasmatic,

Intraventricular, extra ventricular and paraventricular in relation to third ventricle.

Puget et al classified pediatric craniopharyngioma based on pre-operative hypothalamus involvement. (43)

Grade 0 – no hypothalamus involvement

Grade 1 – hypothalamus displaced by the Tumor

Grad 2 – hypothalamus involvement.

Imaging characteristics:

Currently, used tools for diagnosis are MRI with contrast and CT scan. Occasionally, angiography may be used to see vascular relation in large tumor and for surgical planning. X-ray was used previously but that has been replaced by recent imaging methods.

CT scan is ideal for bony anatomy as well as see the calcification of Tumor. Non-contrast CT scan demonstrates suprasellar and often intrasellar mass with calcification and hypodense cystic with isodense solid components. The density of

cystic component usually greater than the attenuation of CSF Contrast enhanced CT scan may show enhancement of solid portion as well as a cystic wall. (45,46)

Craniopharyngiomas appearance on MR imaging depends on the solid and cystic component, the content of cyst i.e. cholesterol, keratin, hemorrhage) and the amount of calcification. Solid component may be iso to hypointense compared to brain parenchyma on T1 WI, the cystic component will be hypo on T1WI and hyperintense on T2WI. Protein and cholesterol cause high signal on T1WI while protein, calcification, and blood products cause low signals on T2WI. Post Contrast image shows enhancing peripheral rim. (47)

Post-operative period neuroimaging is useful to evaluate the extent of tumor resection. Minimal flecks of residual calcification on CT scan without solid or enhancing tumor on postoperative MRI, do not carry an increased risk of tumor recurrence.

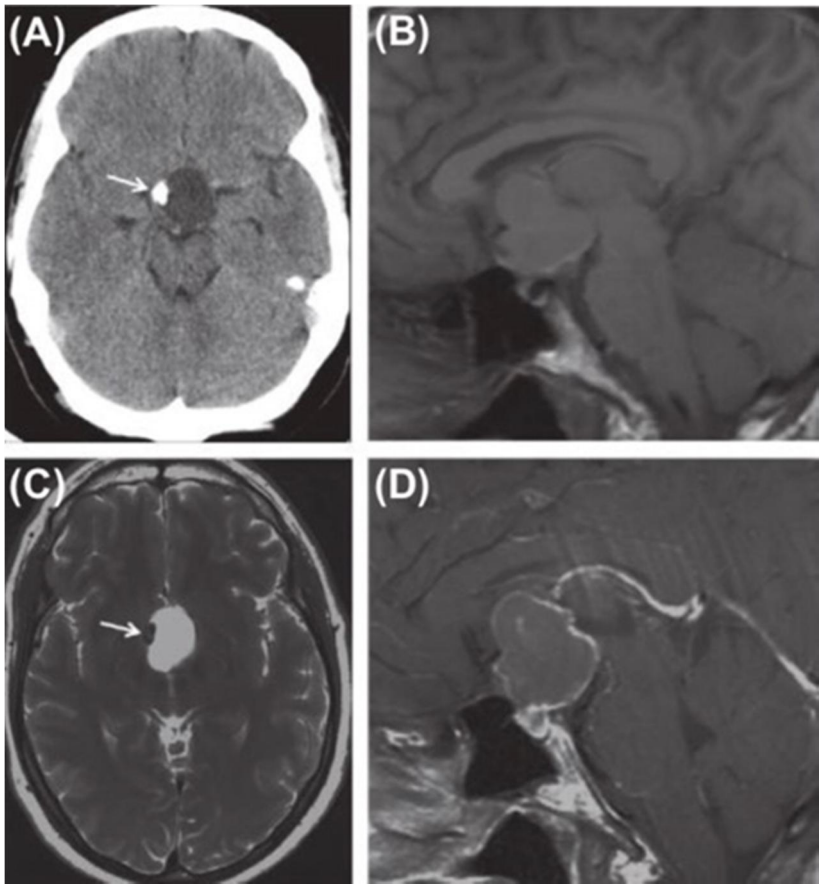


Figure 3: A, Axial, non- contrast CT image shows a hypo dense, suprasellar cystic mass measuring 20 Hounsfield units in density, with a peripheral, nodular focus of calcification (arrow). The calcification is not typically seen with a Rathke cleft cyst. B, Sagittal, T1-weighted MR image shows a lobulated, moderately hyper intense, suprasellar mass. C, Axial, T2- -weighted MR image shows focal hypo intensity (arrow) corresponding to the calcification seen on CT imaging. D, Sagittal, T1-weighted enhanced MR image shows peripheral enhancement of the mass. The enhancement is not typically seen with a Rathke cleft cyst

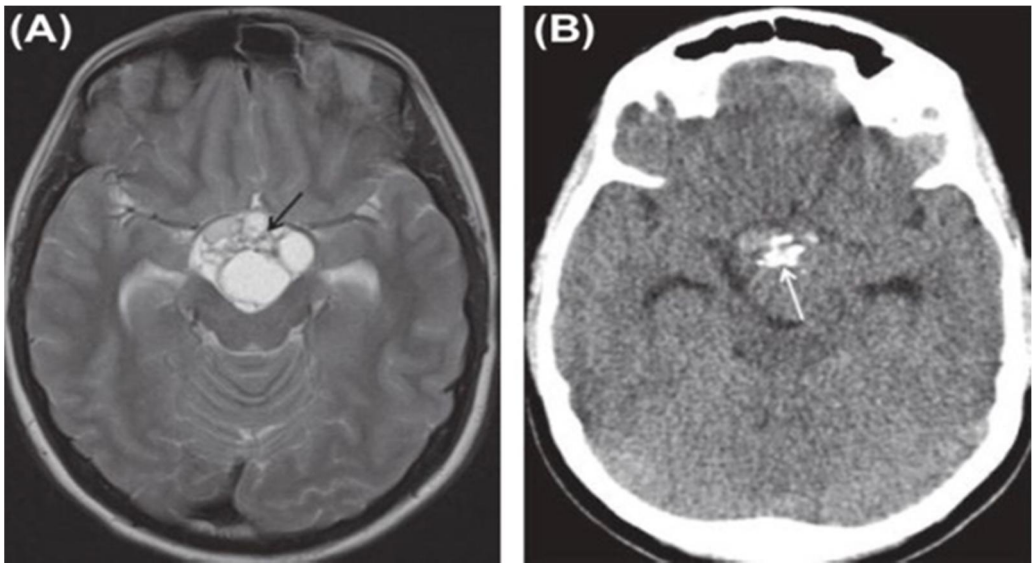


Figure 4: A, Axial, T2- weighted MR image shows a complex, multi cystic, suprasellar mass. The cysts have variable signal intensity, primarily reflecting different protein concentrations. Areas of hypo intensity (arrow) are related to calcification. The mass splays the cerebral peduncles. B, Axial, non-contrast CT image shows calcifications (arrow) corresponding to the areas of hypo intensity on MR imaging.

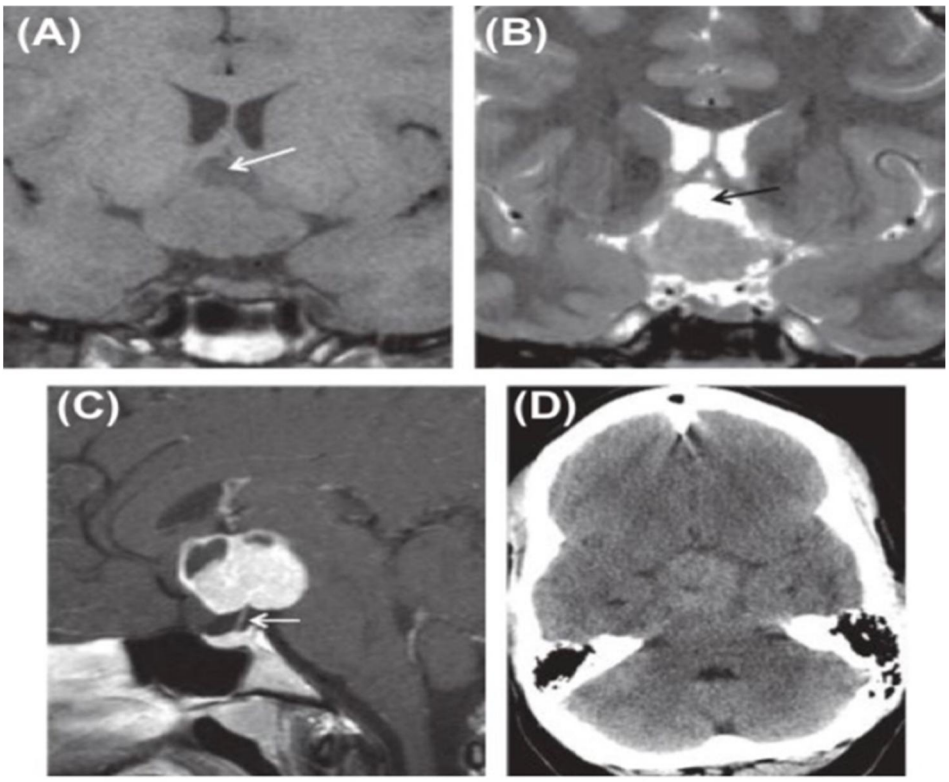


Figure 5: A, Coronal, T1-weighted MR image shows a lobulated, suprasellar mass that is isointense relative to parenchyma; a cystic-appearing portion (arrow) that is only mildly hyper intense relative to CSF is seen superiorly. B, Coronal, T2-weighted MR image also shows a lobulated, suprasellar mass that is isointense to the parenchyma; the cystic-appearing portion (arrow) is hyper intense. C, Sagittal, T1-weighted enhanced MR image shows mostly solid enhancement of the mass. The infundibulum (arrow) is not displaced posteriorly (compare to chordoid glioma, Figure 3.16). D, Axial, non-contrast CT image shows a mass that is isodens to parenchyma; no calcification is seen.

	Adamantinomatous craniopharyngioma	**Papillary craniopharyngioma**	**Rathke cleft cyst**	**Pituitary adenoma**	**Glioma**	**Meningioma**	**Thrombosed aneurysm**
Age	Childhood	Adults	All age	Adult before puberty	Adult	Adult	Adults
Location	Suprasellar	Suprasellar	Intrasellar	Sellar,	Anterior third ventricle	Planum sphenoidale	Suprasellar/parasellar
Calcification	90%	Uncommon	Rare	Rare	Rare	Occasional	Rim
Composition	Solid cystic	Solid	Cyst	Solid	Solid	Solid	Flow void
Enhancement	Solid portion and cyst wall	Heterogenous	Rare	Heterogenous	Homogenous	Homogenous	Variable
Lobulation	Multilobulated	Occasional	Occasional	In large adenoma	No	No	Occasional
Homogeneity	Heterogenous	Relatively homo	Relatively homo	Variable	Homo	Homo	Variable
Overall Appearance	Heterogeneously enhancing, lobulated, cystic, and solid supra sellar mass with calcification	Solid, heterogeneously enhancing, suprasellar mass in	Adult Noncalcified, non-enhancing, intrasellar, proteinaceous cyst possibly with suprasellar	Extension Enhancing intrasellar, or intrasellar and suprasellar mass, inseparable from pituitary	Gland Homogeneously enhancing, third ventricular	Mass Homogeneously enhancing, dural-based	Mass Flow void, blood products of variable signal, blooming onT2* gradient echo

Table 1: Imaging Characteristics of Craniopharyngioma and Other Sellar Region Lesions

Treatment:

The goal of treatment for craniopharyngioma is permanent control or cure. However, the optimal treatment strategy remains controversial, with the debate centered on the extent of tumor resection, role of radiation therapy and other adjuvant therapies.

For symptomatic lesion, surgery is preferred over to wait and watch. Literature reports that patients usually become symptomatic with time. Karavitaki et al reported 12/13 became symptomatic and requires surgical intervention which was kept on follow up. (17)

In case of emergency due to hydrocephalus, it may require urgent intervention for CSF diversion. Sometimes Omaya reservoir also placed in a cystic lesion to install chemotherapy in the future.

In the interest of achieving a good outcome, the various clinician has developed a classification system to select the appropriate level of aggressive care. Puget et al proposed 3 categories based on the extent of hypothalamic involvement and tailored treatment plan accordingly. Some larger studies still advised aggressive resection as the best. (43,44)

Surgical approaches: Although various approaches have been described for the excision of craniopharyngiomas, these can be simplified into the following-*a) transcranial and b) transnasal*

Transcranial approaches-

- Anterior midline approach (subfrontal-tumor strictly in the midline, extended along anterior skull base and suprasellar location)
- Anterolateral (pterional, orbit zygomatic- tumor located in a suprasellar cistern with variable lateral extension)
- Intraventricular (trans-callosal trans-ventricular, trans-cortical trans-ventricular - third ventricular location)

Transnasal approaches-

Endoscopic-Trans-nasal transsphenoidal and extended transsphenoidal approach for purely sellar type and subdiaphragmatic craniopharyngioma.

Here, we have briefly described the transcranial approaches which we have included in our study.

a) Pterional approach:

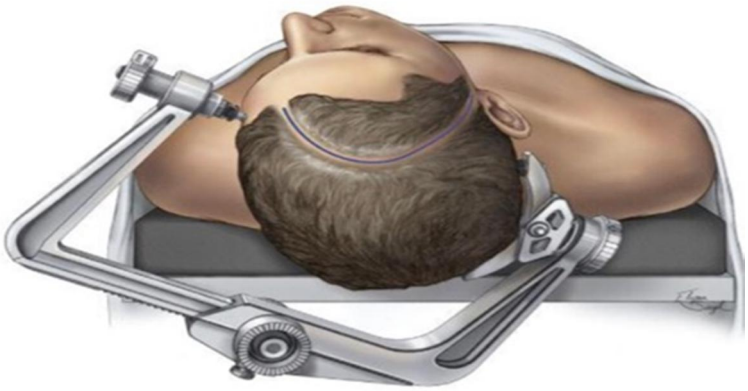


Figure 6A: An illustration of the senior author's incision for a pterional craniotomy. A strip of hair is left anterior to the incision.

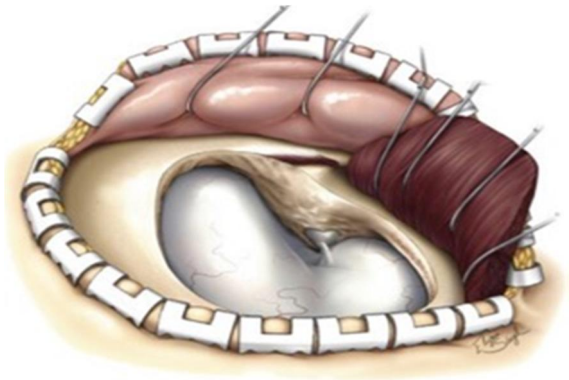


Figure 6B: An illustration of removal of bone and dura exposure.

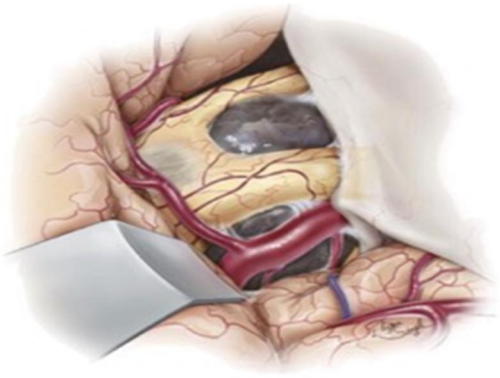


Figure 6c: an illustration demonstrating the various corridors for tumor resection after Dural opening in pterional approach.

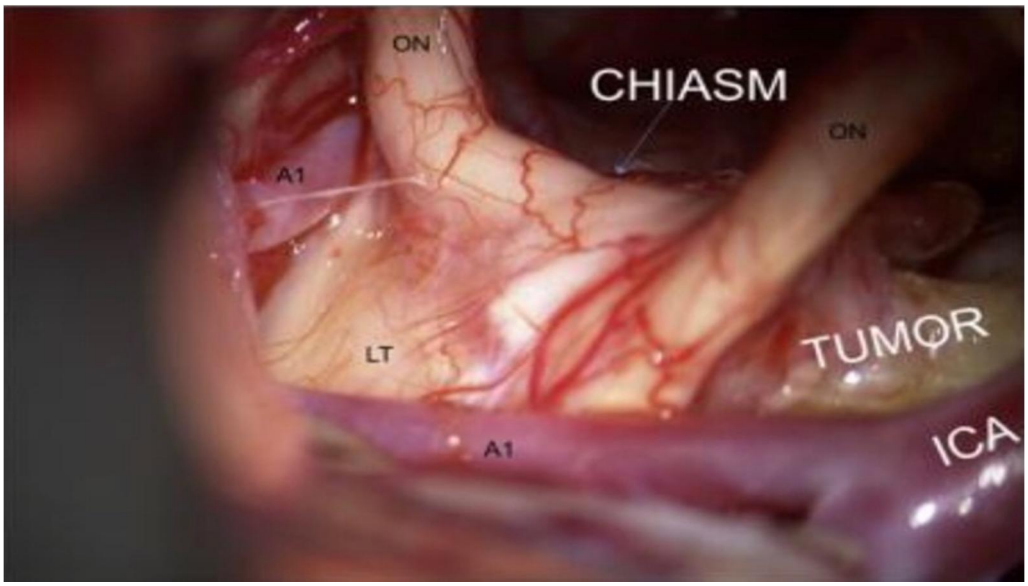


Figure 7: Intra-operative photograph of the pterional approach to a suprasellar craniopharyngioma after partial resection of the tumor. (ICA: internal carotid artery; ON: optic nerve; A1: First division of the ACA.)

B) Inter hemispheric approach:

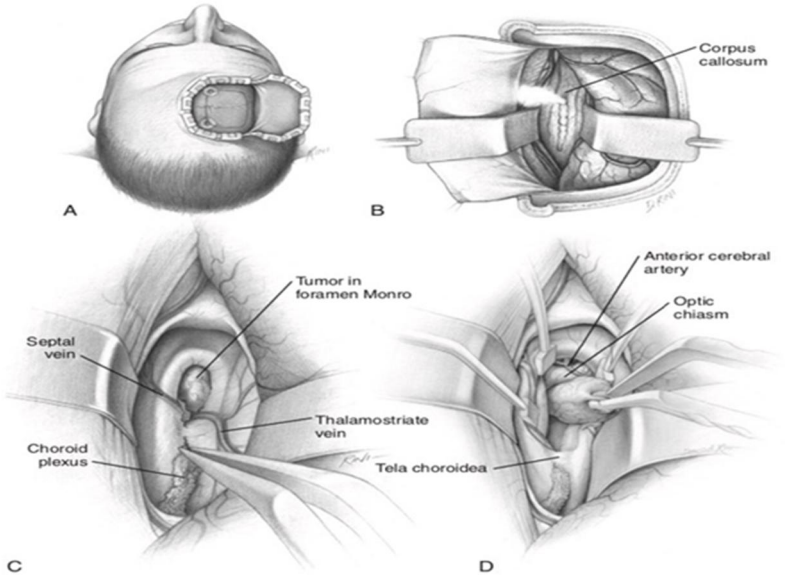


Figure 8: Inter hemispheric trans- ventricular approach. A, A bone flap two thirds anterior and one third posterior to the coronal suture is cut with a craniotome. The frontal lobe is retracted from the falx and cingulate gyrus until the peri callosal arteries and corpus callosum are exposed. B, A 2- to 3-cm callosotomy is performed to enter the lateral ventricle. C, the choroid plexus and thalamostriate vein are followed to the foramen of Monro where the tumor is identified. The choroid plexus and thalamostriate vein are coagulated and sectioned. D, the choroidal fissure is opened to remove the tumor. (From Mayfield Clinic, Cin- cinnati, OH.)

MATERIALS AND METHODOLOGY

Study group: From the years 2017 to 2019, in the Department of Neurosurgery, SCTIMST, Trivandrum, we performed a prospective study to assess the difference in the outcome of craniopharyngioma operated trans-cranially by different approaches. This prospective study was started after getting IEC clearance. We included a qualified neuropsychologist for the detailed evaluation of pre and post-operative neuropsychological assessment.

A total of 18 consecutive patients were included in this study, who met the inclusion criteria. All patients were divided into two groups= Group A: operated via interhemispheric Trans callosal approach. Group B: operated via pterional trans-sylvian approach. We selected all symptomatic patients with an age of more than 2 years. Results were compared in the form of neuropsychological outcome, morbidity as well as mortality. All patients were followed up at 2 weeks following surgery, 1-month, 3-month, 6-month, 1 year and later according to the clinical condition. Some patients with electrolyte imbalance were advised for frequent follow-up. We advised all patients to consult an endocrinologist for hormonal therapy once stabilized from the neurosurgical side.

Inclusion criteria :

- Age of more than 2 years.
- Both sexes.
- the predominant suprachiasmatic extension

Exclusion criteria :

- Age more than 50 years
- Those who are presented with acute symptoms like hydrocephalus or poor sensorium which requires urgent management.
- Recurrent cases excluded.

- Prior adjuvant therapy if taken.
- Predominant intrasellar component which is suitable for trans-nasal trans-sphenoidal approach.

Funding: We have used the fund for prospective study with institutional permission with ref no 5453.

Workup plan: All patients underwent basic investigations like blood group, routine blood investigation, X-ray chest, ECG and 2D-Echocardiography if age more than 40 years for cardiology fitness. MRI brain with contrast if not done recently within 6 months. On admission, we have done a CT scan to see bony anatomy, calcification and to rule out acute sequelae. Post-operatively, all patients underwent hormonal status and visual field and visual acuity charting and MRI after 6 weeks to see residual and decide a further plan.

All patients underwent neuropsychological assessment. Neuropsychological tests were applied preoperatively, post-operative within 1 month and follow up after 3 months. For children, we performed a ray auditory verbal learning test (RAVLT), visuospatial working memory span task, and Wechsler intelligence scale for children (WISC-IV). For adults, we performed frontal and temporal memory subtest of NIMHANS battery and Wechsler adult intelligence scale (WAIS-IV). Behavioral observation was done in all cases. Patient(s) who didn't co-operative for neuropsychological examination were also noted. Post-operative co-operation for test was considered significant behavioral changes. Each neuropsychological battery provided a score and pre-operative scores were compared with post-operative scores. We performed the test on OPD basis for the patients who were stable and awaited elective admission. Post-operatively, once a patient is out of immediate complication and is stable enough to co-operate for the tests, we administered the neuropsychological battery. For children, test was individualized by the neuropsychologist and the test most frequently given was also compared at the end. An overall rating of neuropsychological function was determined for each child, including assessment of intelligence, memory, language, visuospatial function, frontal lobe, temporal lobe function and behavior.

RESULTS ANALYSIS

Patient characteristics: A total of 18 consecutive patients were included in the study over a period of 2 years following IEC clearance. Out of these, 9 cases were male, and 9 cases were female. The minimum age was 3 years and the maximum age was 34 years. The mean age was 14.31 years. In Inter-hemispheric group, 6 males and 2 females were present, while in pterional group, 3 males and 7 females were present.

Clinical course: The most common presentation in this study was headache (14 patients) followed by vomiting (8 patients), visual disturbance (10 patients), hormonal disturbance (5 patients). 2 cases were detected incidentally, one following trauma and other, while undergoing evaluation for headache.

The mean duration of symptoms was 8.5 months (less than 1 month to 36 months). In Inter-hemispheric group, the mean duration of symptoms, at admission, was 3.4 month (less than 1 month to 6 months). In pterional group, the mean duration of symptoms was 13.82 months (less than 1 month to 36 months)

A) *Hydrocephalus*: 7/8 cases in the interhemispheric group showed hydrocephalus, while 5/10 cases in pterional group demonstrated hydrocephalus. In Interhemispheric group, lesions were mostly confined within 3rd ventricle with a predominant suprasellar component, which is the probable cause of hydrocephalus.

B) *Seizure:* only 1 patient presented with seizure in which tumor size was more than 3 cm in all direction.

C) *Endocrine deficiency* : 2 pediatric patients were evaluated for short height and were found to have low GH as well as low IGF value. 10 patients had low cortisol value below 10mcg/dl (cut off for normal). All patients were given steroid supplement peri operative and post-operative period.

D) DI: 3 patients had polyuria and polydipsia preoperatively. However, electrolyte imbalance was not found on evaluation.

Surgical characteristics: 8 patients underwent excision using Interhemispheric transcallosal and 10 cases underwent excision by pterional approach. All patients underwent gross total excision.

Intra operative events: No major intra-operative events were noted, including neuro-vascular injury.

Post-operative morbidity: Almost all cases had developed Diabetes Insipidus post operatively. In the acute stage due to major fluctuation in Sodium balance, we have managed with vasopressin SC or IV doses along with the oral fluid correction. Almost all patients were started oral feed as soon as they are out of the post-anesthesia effect. In case of a pediatric patients who were unable to take orally, we preferred to put Ryle's tube (nasogastric tube) along with IV fluid supplementation for correction of fluid. Once the patient was stable and maintained electrolytes balance with oral correction he/ she was planned for discharge.

Post-operative mortality: One patient expired in our study in an interhemispheric group. Post-operatively, his GCS remained low and he was tracheostomized and was given aggressive treatment. However, due to severe hypothalamic dysfunction, he could not survive beyond post-operative day 5.

Neuropsychological characteristics:

In interhemispheric group, subject-4 was not cooperative pre-operatively but after the surgery, his behavior improved. So, postoperative and subsequent follow up neuropsychological evaluations were done. One subject had significant loss of vision in both the eyes, so the neuropsychological evaluation could not be performed. So, for 6 patients (out of 8) neuropsychological data was available for comparison which is plotted on a graph.

In pterional group, 1 subject was lost for follow up after surgery due to personal reasons. So only 9 subjects were available for neuropsychological evaluation. Available data is plotted on graphs as shown below.

Memory: function for Temporo- parietal lobe

Digit span: Memory span is the longest list of items that a person can repeat back in correct order immediately after presentation of 50% trial, which may include numbers, words, etc. It is called digit span, when it includes the numbers. It measures short term memory. It measures working memory's number storage capacity. In the interhemispheric group and pterional group, digit span score seems to be increased. Patients were able to retain more number, which was suggestive of improvement in working memory. However, pre-operative and post-operative score of digit span had no significant difference statistically.

Paired association: Paired association is the ability to remember and recall specific events paired with the context in which they occurred. It assesses episodic memory. It measures temporal lobe function. It is improved in the interhemispheric group. Neural plasticity is the basis of associative memory formation. (54)

RAVLT (Rey Auditory Verbal Learning Test): It evaluates a wide group of functions: short term auditory-verbal memory, rate of learning, learning strategy, retention of information and difference between learning and retrieval. It is impaired in medial temporal injury. Temporal lobe retractions are common during pterional trans-sylvian approach. So, there is a high chance of auditory verbal learning dysfunction. However, in our study, there was an improvement in the interhemispheric group and pterional group, except in one patient, in whom immediate and delayed recall was decreased after surgery. This patient had a viral infection and hospitalized for another reason not related to surgery and was on recovering phase during the examination.

Ray figure complex: It measures incidental memory. Here, the patient sees an image and then draws that image from his memory (recall). It assesses visuospatial ability, memory, attention, working memory, and executive function. It includes both immediate and delayed recall. In both the interhemispheric and Pterional group, it showed improvement after surgery.

Frontal lobe and executive function test:

Test for attention: a) focused attention by the color trail test. The test consists of two parts called Trail A, and Trail B. First part includes connecting dots as rapidly as

possible. The second part consist of connecting the alternate number with alphabets. This provides information about visual search speed, scanning, processing speed and mental flexibility. It is an important component of cognitive function. Both Interhemispheric and pterional group showed improvement in executive functions post-surgery.

B) Digit vigilance test (test for sustained attention): This measures rapid visual tracking and accurate selection of the target. It focuses on alertness and focused concentration while giving fewer demands on other components – capacity and selectivity. In interhemispheric and pterional groups, digit vigilance error reduced after surgery.

C) Triads: (Test for divided attention): Here, two different stimuli are delivered to the patient and how accurate an attention to both the stimuli the patient is giving, is measured by triad test.

D): Digit symbol substitution test: This another set of tests measures the speed of processing, sustained attention and visual-spatial skill. It also used in Wechsler adult intelligence score. Improvement is seen after surgery in the interhemispheric and pterional group.

Test for working memory:

a) it includes N back visual and N back verbal memory test (verbal and visual working memory). Working memory measures limited capacity that is responsible for temporarily holding information available for processing. It is useful for the short-term memory.

b) self-ordered pointing test: The self-ordered pointing test (SOPT) was developed by Petrides and Milner (1982) as a test of working memory for patients with frontal lobe lesions (55). The task includes a set of pictures of familiar objects or abstract designs, arranged in a grid. These are presented in a different spatial arrangement on each trial and the participant is required to point to a different picture every time. The test requires executive abilities to organize and carry out a sequence of responses as well as to retain and constantly monitor the responses made. Post-operative score in the pediatric patients was reduced for verbal and visual working memory test but

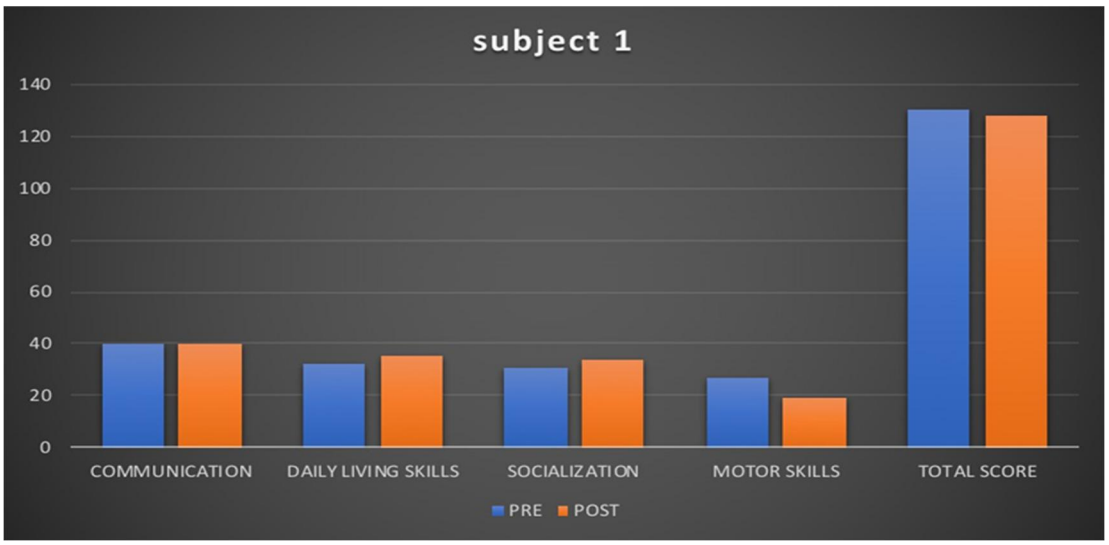
improved on follow up examination, suggestive of no deterioration on follow up in both study group after surgery.

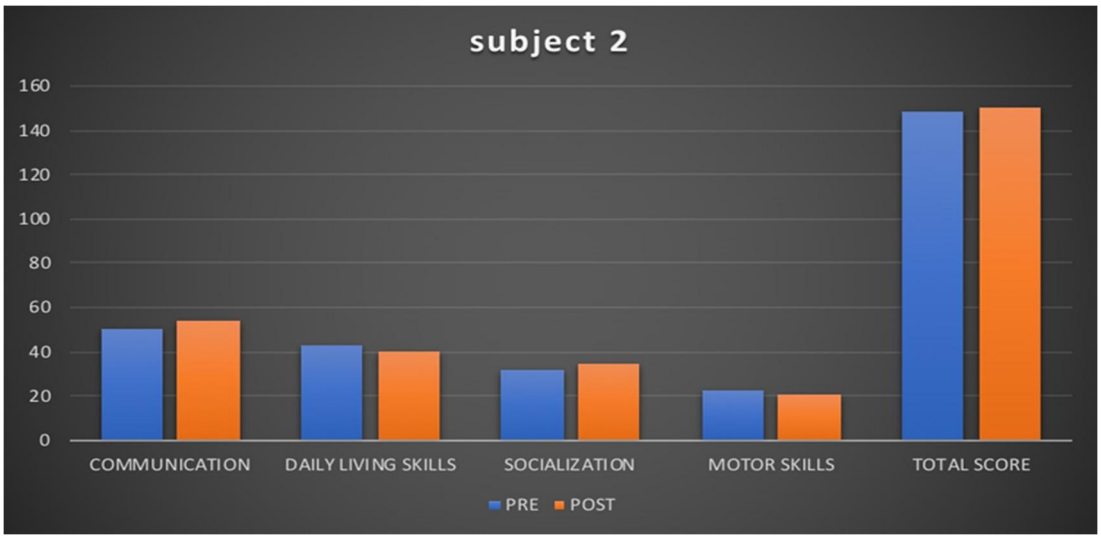
Strop test: It is an important component of executive function of frontal lobe mediated by anterior cingulate gyrus. Strong inhibition and attention is required for this test. Post-operative score in the interhemispheric group and in a pterional group showed improvement.

Test for executive function: It includes a) Fluency test and b) Category Fluency-Animal names test. This measure executive function of the frontal lobe. Postoperative improvement was seen in interhemispheric and pterional group following surgery.

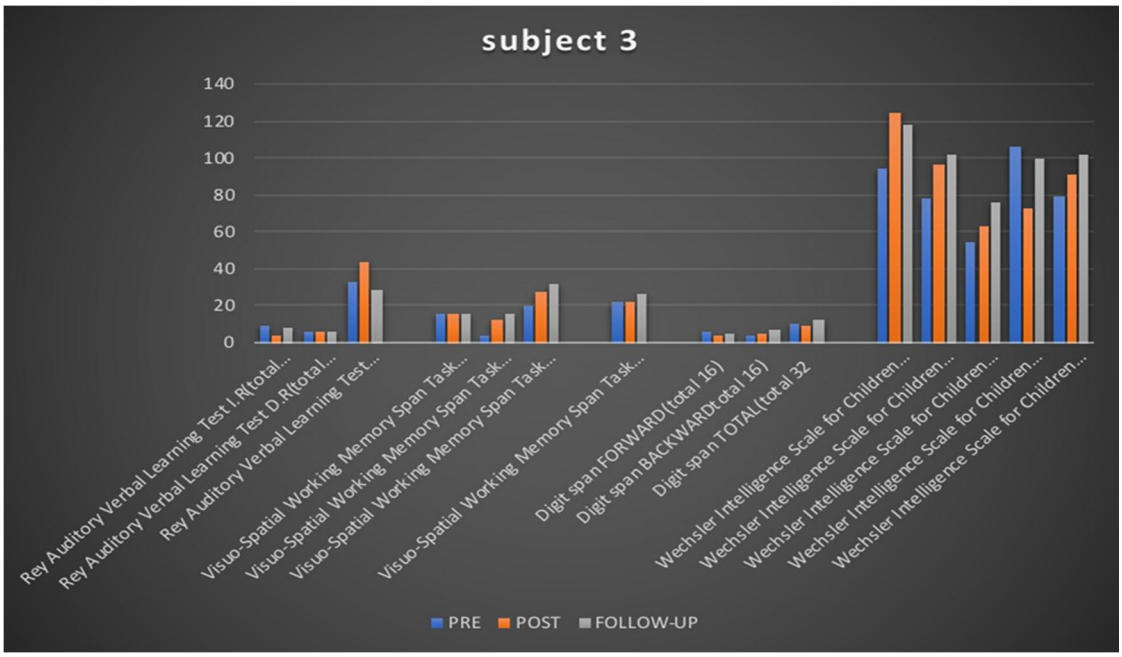
IQ test: WISC IV: verbal intelligence was assessed using the Wechsler intelligence scale for children which itself contains multiple components. The intelligence quotient score was calculated from the score. (56,55) We noticed no deterioration in IQ of an individual operated either by trans-sylvian or interhemispheric approaches. IQ remains within the normal range following surgery.

Inter hemispheric group:

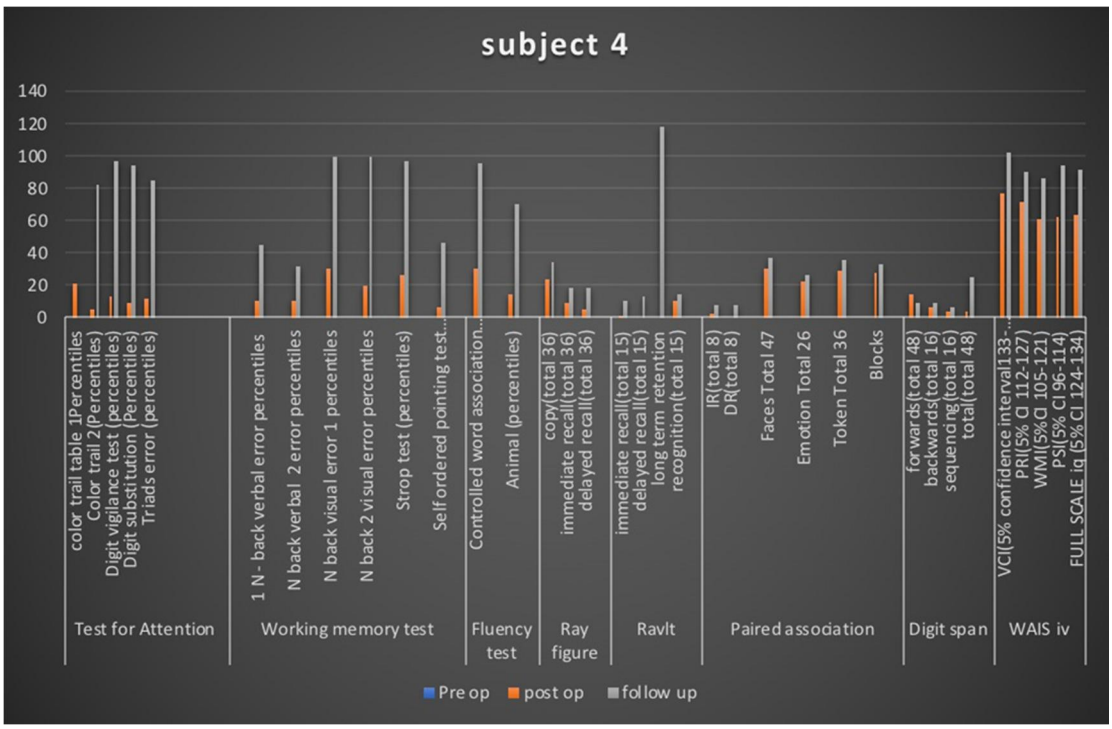


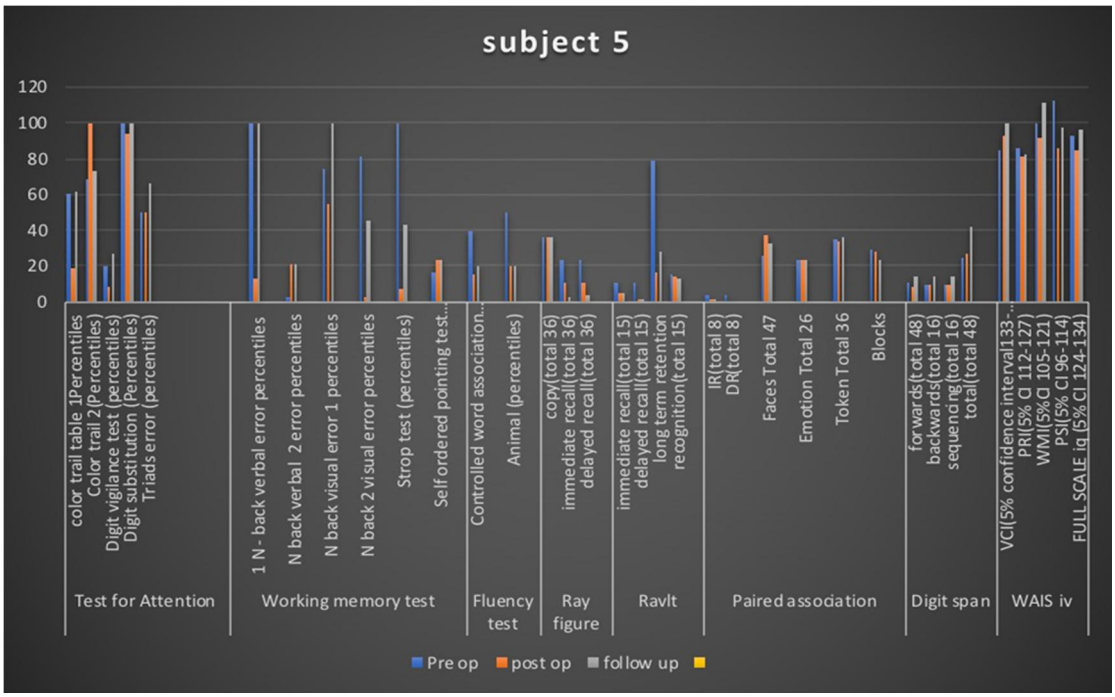


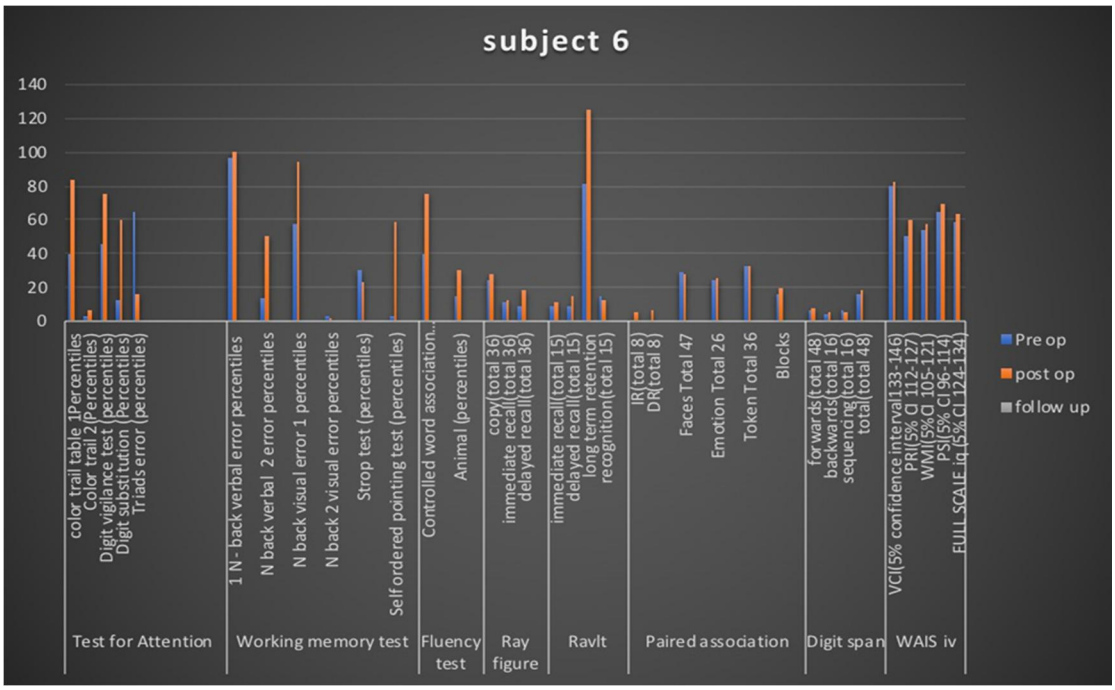
Graph 1 and 2: showing neuropsychological characteristic of pediatric patients with age below 5 years operated by inter hemispheric approach.



Graph 3: showing neuropsychological characteristics in pediatric patients with age 13 years operated by inter hemispheric approach.

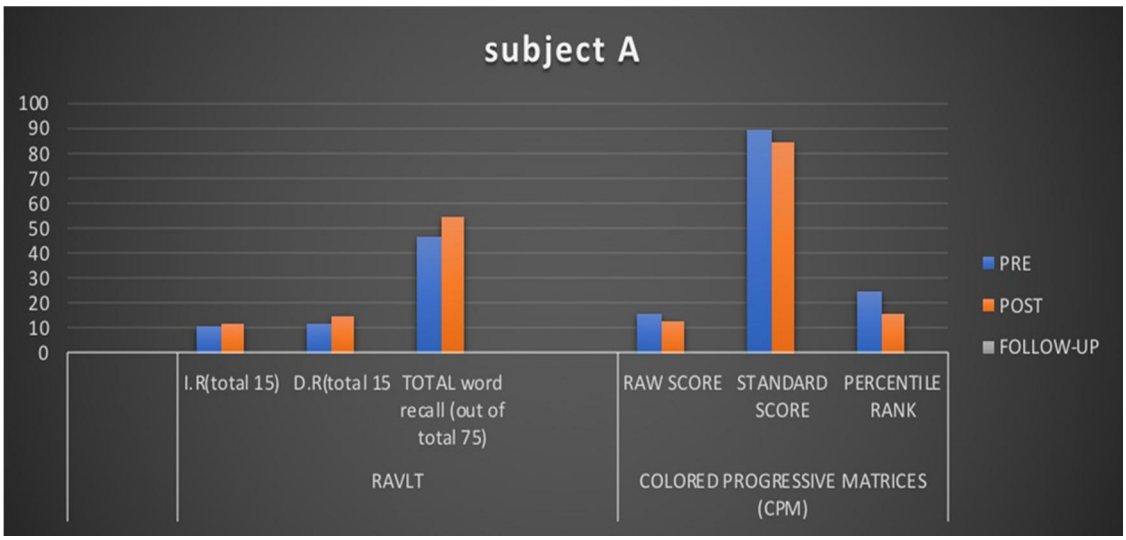




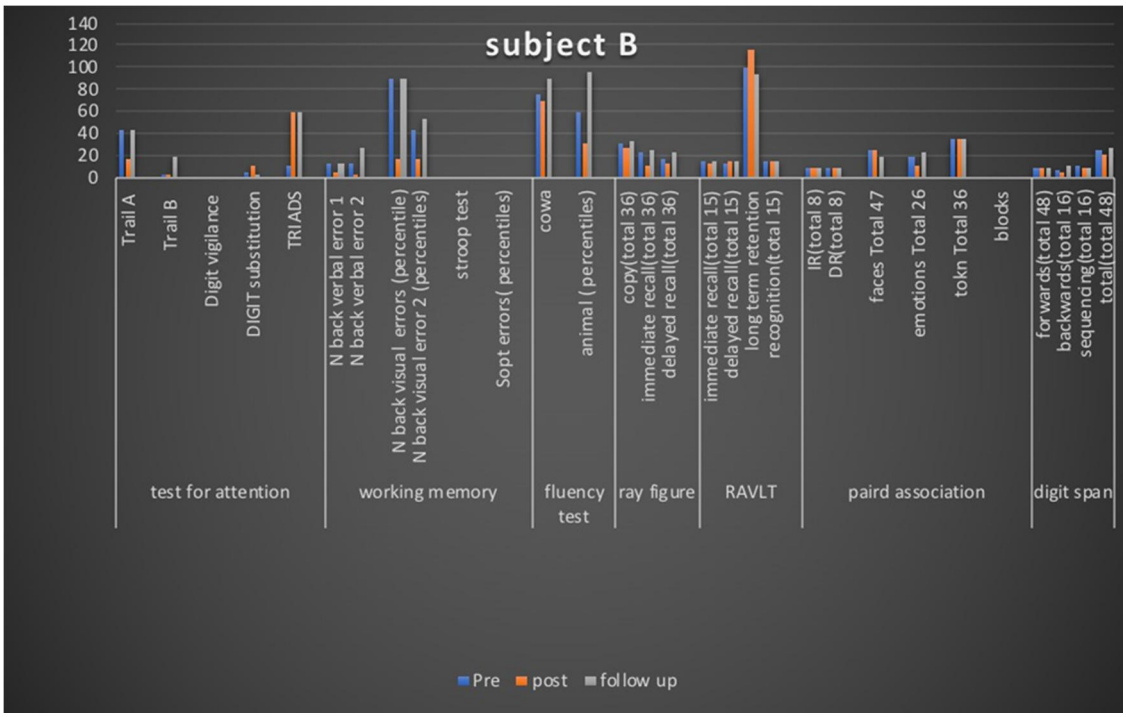


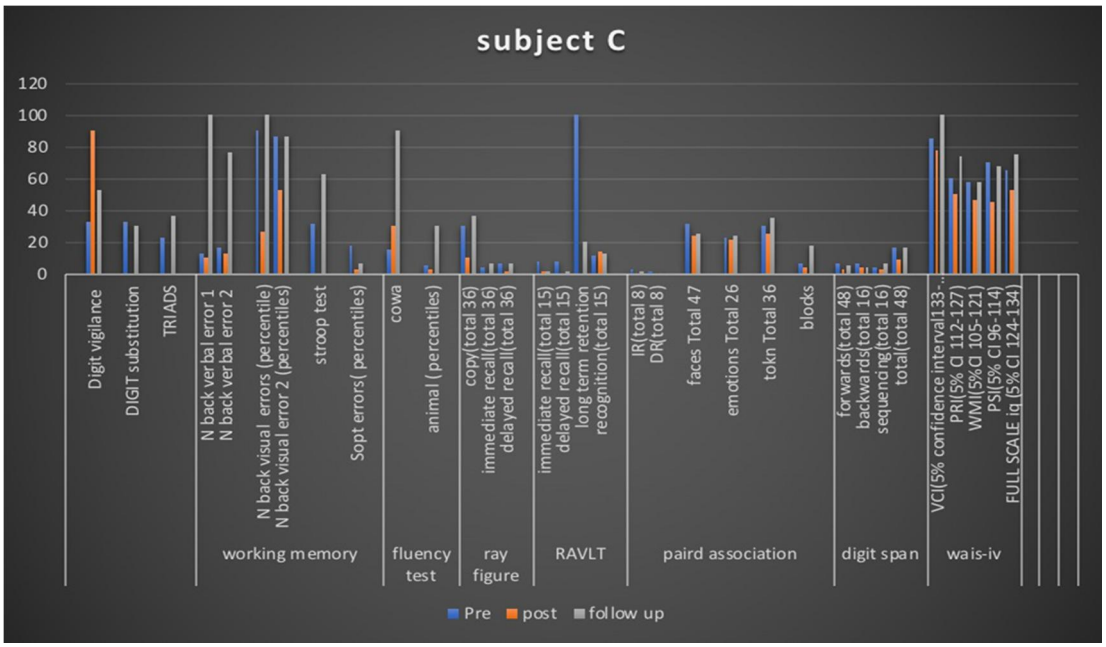
Graph 4-6: showing neuropsychological characteristics in adult population with age above 20 years operated by inter hemispheric approach.

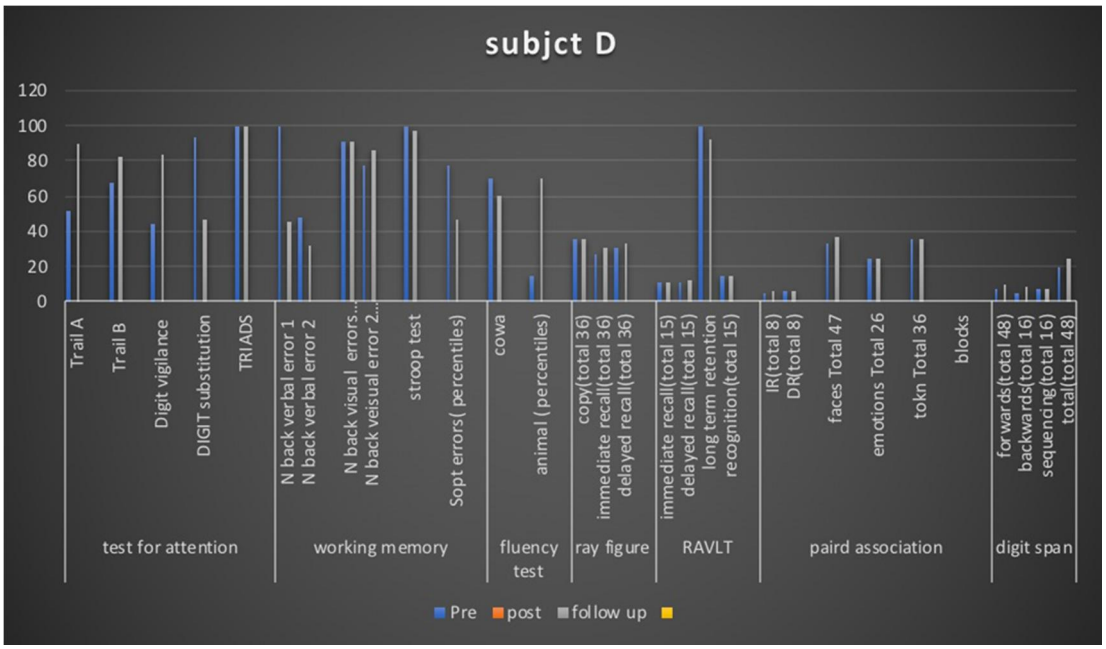
Pterional group:



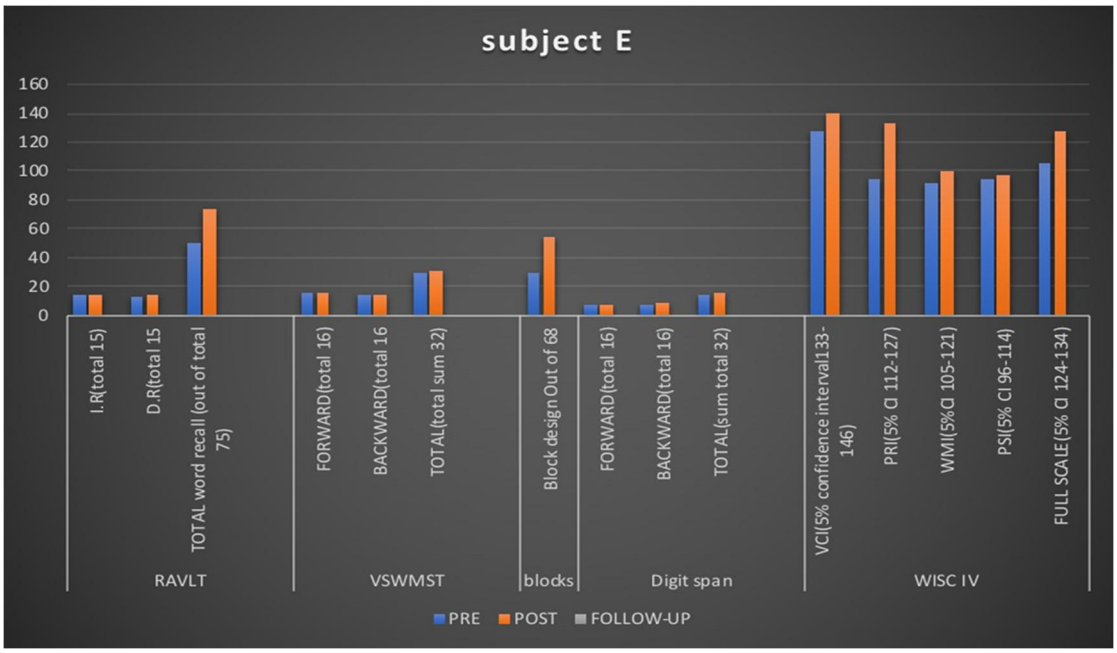
Graph A: showing neuropsychological characteristics of pediatric patient with age 5 years operated by pterional approach.







Graph B, C and D: showing neuropsychological characteristics in a patient operated by pterional group with age more than 12 years


subject E
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I.R(total 15)
D.R(total 15
TOTAL word recall (out of total 75)
FORWARD(total 16)
BACKWARD(total 16
TOTAL(total sum 32)
Block design Out of 68
FORWARD(total 16)
BACKWARD(total 16)
TOTAL(sum total 32)
VCI(5% confidence interval 133-146)
PRI(5% CI 112-127)
WMI(5% CI 105-121)
PSI(5% CI 96-114)
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Digit span
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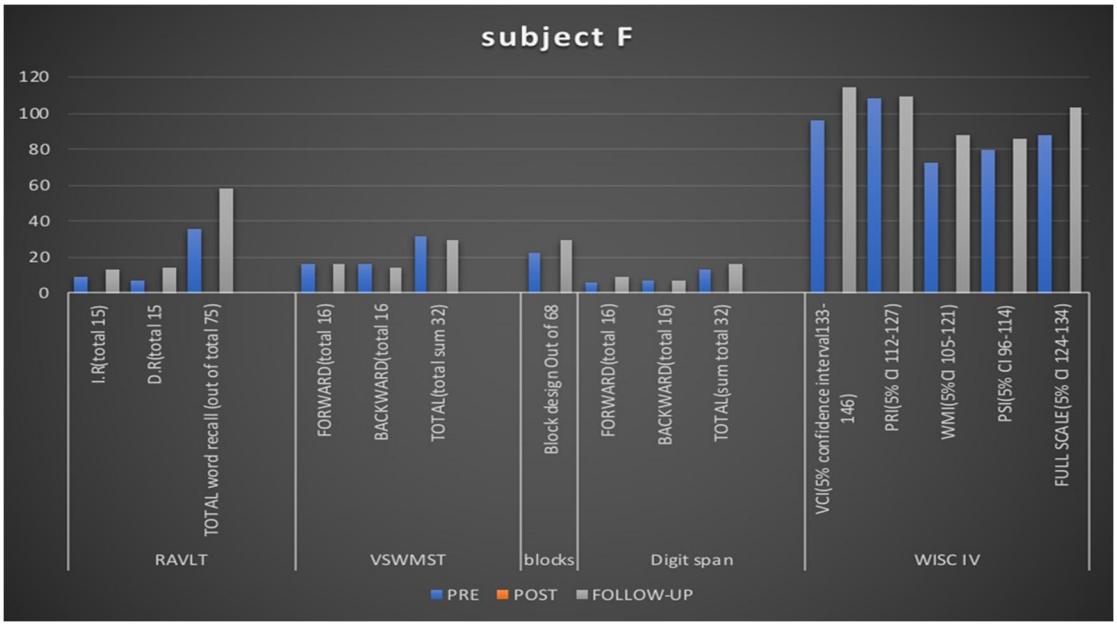
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TOTAL word recall (out of total 75)
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TOTAL(total sum 32)
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BACKWARD(total 16)
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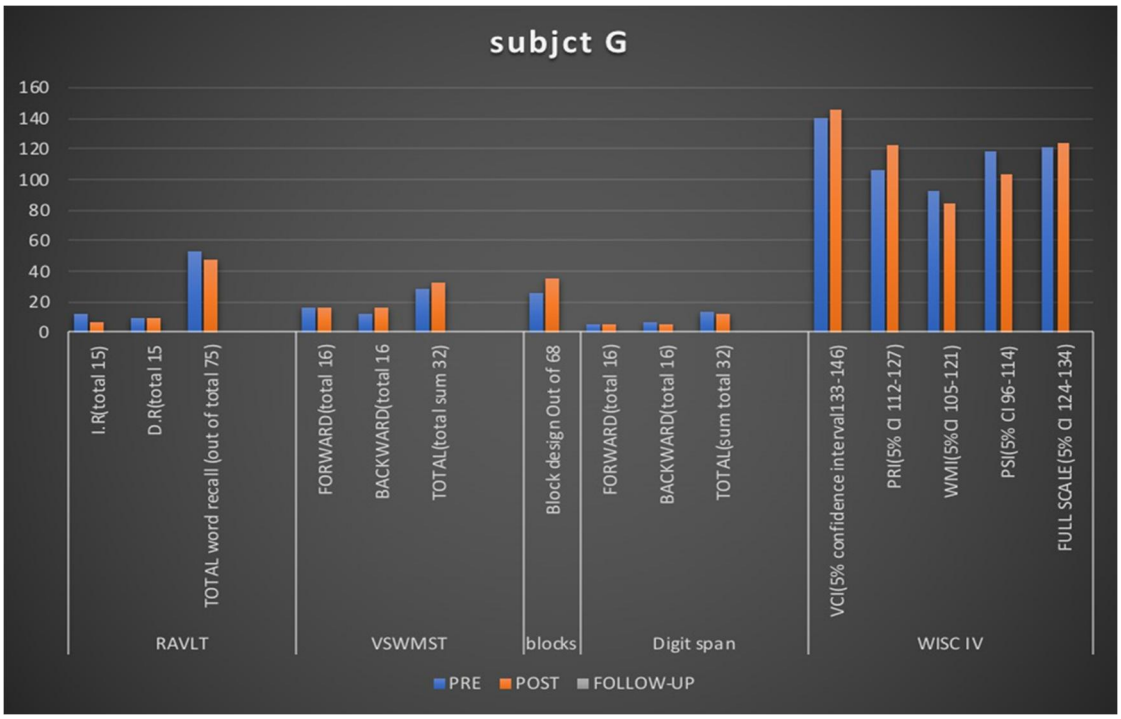
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BACKWARD(total 16
TOTAL(total sum 32)
Block design Out of 68
FORWARD(total 16)
BACKWARD(total 16)
TOTAL(sum total 32)
VCI(5% confidence interval133-146)
PRI(5% CI 112-127)
WMI(5%CI 105-121)
PSI(5% CI 96-114)
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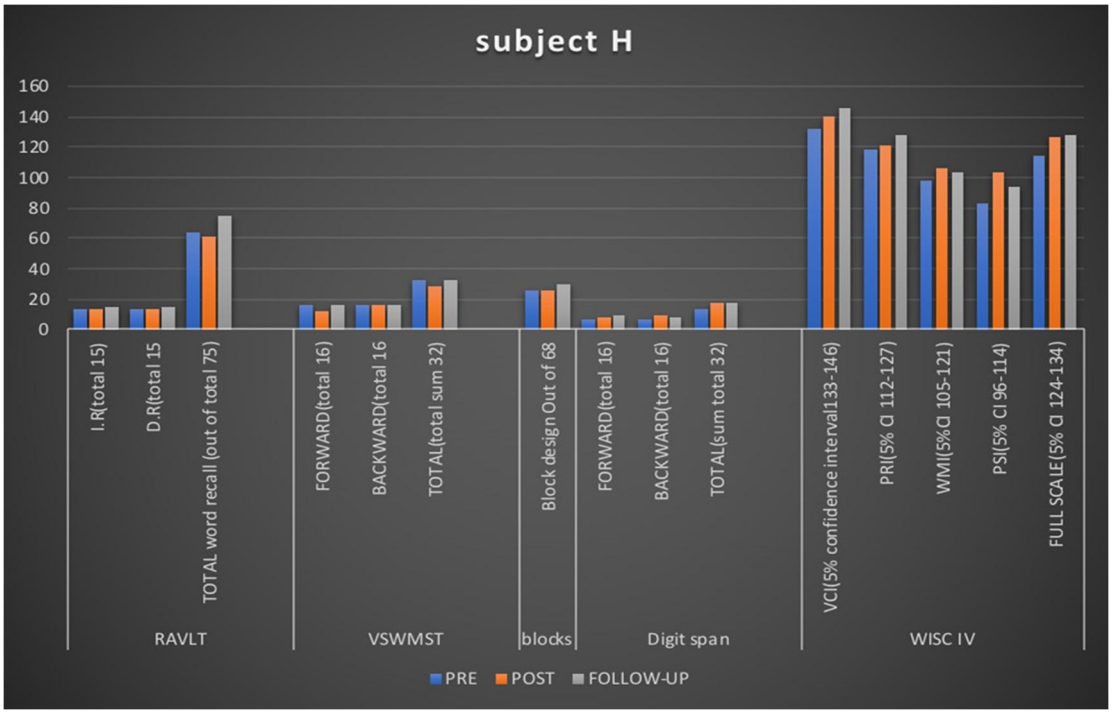
subject H
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D.R(total 15
TOTAL word recall (out of total 75)
FORWARD(total 16)
BACKWARD(total 16
TOTAL(total sum 32)
Block design Out of 68
FORWARD(total 16)
BACKWARD(total 16)
TOTAL(sum total 32)
VCI(5% confidence interval133-146)
PRI(5% CI 112-127)
WMI(5%CI 105-121)
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RAVLT
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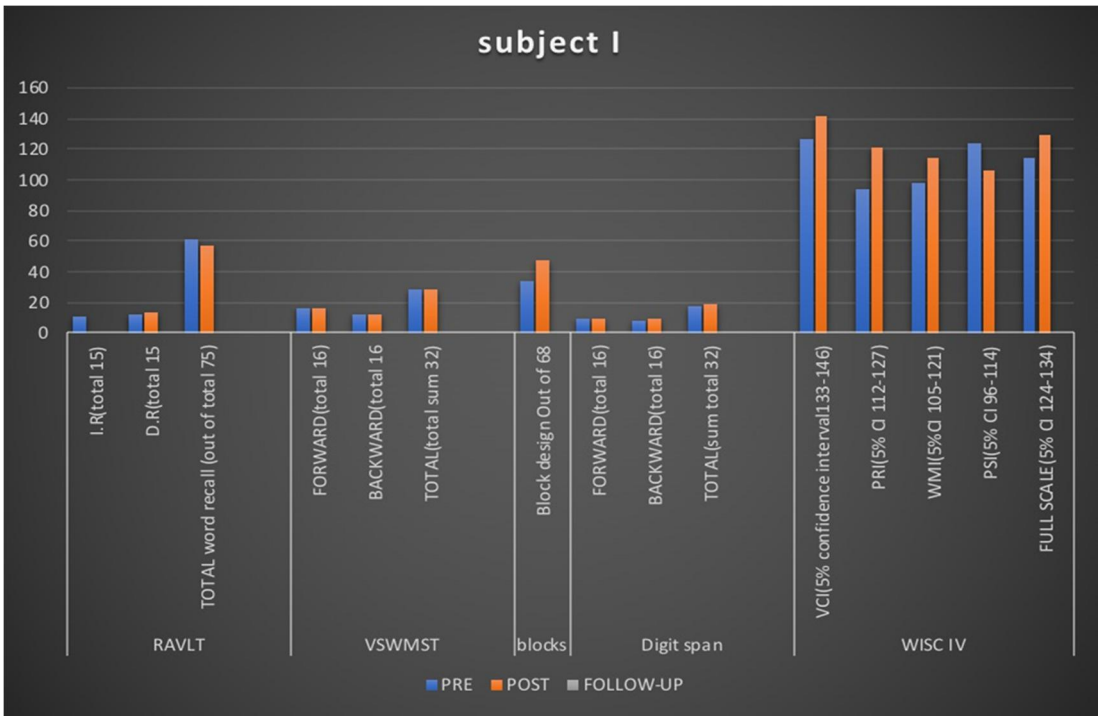

Graph E-I: showing neuropsychological characteristics of pediatric population between 8-13 years of age operated by pterional approach.

DISCUSSION

Surgical approach to craniopharyngioma depends mainly on their location and the surgeon's preference. Transcranial approaches are usually preferred due to the nature of the pathology. Most commonly used approaches are frontal and pterional. (57–59)

Bifrontal interhemispheric approach is one of the widely used approaches. Using this approach, trajectory exposes frontal lobe which is at risk of injury and patients showed frontal lobe dysfunction following surgery. Recently, in the microsurgical era, the interhemispheric transcallosal approach is gaining popularity. Previous retrospective studies have shown preservation of frontal lobe function following total excision. (49) However, in our study, none of the patients showed abnormal behavior following total excision operated by both different approaches.

This study aimed to study the neuropsychological outcome following two different approaches of craniopharyngioma. A various literature study had shown neuropsychological deterioration following interhemispheric approach. This is due to the injury to the corpus callosum fibers. However, the transcallosal approach is one of the best access for third ventricle lesion and it doesn't seem to be associated with cognitive function. (59,60). However, no report appears to have considered, the attentive function which is clearly defective after longitudinal callosotomy seen after epilepsy surgery (60). Because of this, neuropsychological evaluation centered around complete cognitive function. Since the introduction of operating microscope, surgical results have improved with better visualization of anatomical and microvascular structures. Improvement in clinical status also led surgeons to investigate in functional as well as neuropsychological outcomes.

In our study total, 8 consecutive cases were included in the interhemispheric group. Post-operative neuropsychological evaluation was not possible in two cases. Out of these, one patient died on post-op day 5 and the second patient was a child with poor visual acuity pre-operatively which remained the same postoperatively. Remaining 6 cases were evaluated for neuropsychological outcomes, both in preoperative and postoperative period.

NIMHANS battery was applied in 3 adult cases who showed significant improvement in frontal and temporal lobe functions, as compared to pre-operative function. None of them showed any short term spatial or verbal memory deficit. The attention capacity of all patients was good including pediatric patients. Visuo-Perceptual performance of all the patients was good. IQ also improved in all patient. except for one patient in whom fluency decreased compared to preoperative status. He also had difficulty in recall which was seen in decreased score in RAVLT and paired association test. However, overall IQ test showed mild improvement in IQ.

Approaches to the third ventricular tumors have been associated with a lot of challenge to the surgeons. Neuropsychological consequences following disruption of interhemispheric pathway was described by Zaidel, which provided a platform for others to work on interhemispheric approaches and refine callosal resection. (61,62)

One patient was not cooperative for pre-operative neuropsychological evaluation. He demonstrated anger and irrelevant talk during the preoperative assessment. However, post-operatively, neuropsychological assessment and follow up assessment showed good cooperation and significant improvement in score. This suggests that inter-hemispheric approach is not associated with deterioration of neuropsychological function, but it is the nature of the tumor which causes dysfunction. The unmotivated fits of anger and poor cooperation usually have a clinical/anatomical correlation with the hypothalamus, owing to its known connections with the limbic system. (49,58,63,64)

The intelligence quotient (IQ) is a strong parameter for the intellectual function. In the literature, postoperative IQ scores were mostly in the normal range (63), while some cases with postoperative decreased intelligence and retardation have been reported (58). Cavazutti et al noted no significant difference in postoperative IQ, whether radical surgery or limited surgery was performed. (49,64–66) Preoperative IQ scores were available from six patients in a study by Galatzer et al and were not different from postoperative scores. (67) These studies show similar findings as in our study, which demonstrated that verbal IQ is not affected by surgical approaches.

Evaluation of IQ scores in craniopharyngioma patients in preoperative and postoperative period suggested improvement of at least 10 points or remained the same as pre-operative status (within normal range). Parent's descriptions about intellectual performances of children before the operation located them within the normal range, so we can reasonably conclude that there was no significant worsening of the intellectual and neuropsychological functioning for any of the children in the interhemispheric group as well as in pterional group. Though one child in interhemispheric group and one in the pterional group had preoperative as well as postoperative same visual disturbance in which scholastic performance could not be tested.

Postoperative scholastic performance depends on familial support. Following surgery, there will always be conscious or subconscious fear of seizure, tumor recurrence and child will still be sick as he is on hormone replacements. However, in our study 3 patients were from pediatric age group in the interhemispheric group and 8 in pterional group and they did not show any deterioration in scholastic performance.

Riva et al reported personality changes among children with a marked tendency toward depression and frustration. This is possibly due to two reasons, first is due to the long duration of lesion which requires continuous endocrinological and neurological monitoring which give rise to a state of continuous alertness and the second reason could be due to the frustrating experience of body image and obesity in this modern aesthetic world. (68,69) As we have a patient with short term follow up it is difficult to comment. However, within these short durations, no depressing features were observed in either of the study groups. We are following up these patients for other symptoms also.

Frontal lobe dysfunction: The frontal signs in everyday behavior and executive abilities were correlated with radiological evidence of a direct frontal lobe trauma by Riva et al (68) However, frontal lobe dysfunction can occur in Third ventricular lesion also. From the extensive literature, we know that there are substantial efferent projections from the frontal cortex to the hypothalamus and preoptic region, so a hypothalamic injury may also be the cause of frontal-type disturbances (70, 71, and 72)

Nauta et al have demonstrated the presence of projections from the Orbito-frontal surface to the hypothalamus, and children were obese in these series which is consistent with this hypothesis. (70) (72)

Frontal lobe dysfunction was also demonstrated in patients operated by sub frontal approach in a high percentage of patients by Cavazzuti. (49) Probable reasons for morbidity could be the fact that the author had included patients operated during the pre-microsurgical era.

Word fluency and spontaneity, which were assessed by the Controlled word association and animal count test, are anatomically related to the orbitofrontal area. This area is retracted during a subfrontal approach but it is also dependent on other frontal areas. We demonstrated preserved word fluency after surgery in the interhemispheric group and in the pterional group. Preoperative and postoperative results of individual patients were highly congruent. Cavazutti et al also demonstrated a normal postoperative word fluency after craniopharyngioma surgery in the presence of other neuropsychological dysfunctions (49).

Attention: Trail test, digit substitution, strop test are important tests demanding measures of attention, concentration, and cognitive speed. Strop test measures strong attention and inhibition function of the frontal lobe (anterior cingulate). It requires intact frontal lobe and independent memory function. Subject requires time to take the decision for task execution. The timing to take decision and task execution is measured. Longer time is required if the frontal lobe function is impaired. In the interhemispheric approach, working area is near cingulate gyrus so likely to be injured during hemisphere retraction. However, in our study, attention and working memory were not affected in interhemispheric group. In pterional group also, this executive function was not affected by surgical approach. This suggests that craniopharyngioma itself is the most likely cause of impairment of cognitive functions. Craniopharyngioma interrupts reciprocal projections between the frontal lobes and the hypothalamus. Alternatively, they might encroach on fronto-dorsal areas either directly or by brain edema. (73–75)

Hydrocephalus: There are many variables that may have influenced these results. As far as age is concerned, the tests administered did not reveal any behavioral

differences although the children were treated between the ages of 2 and 14 years. There were no effects due to hormonal alterations because all the children were well compensated from this point of view, as shown by their good level of attention and mental behavior. Regarding hydrocephalus, both experimental (76) and clinical studies (77) have shown that only chronic and persistent increase in pressure has a detrimental effect on the cerebral parenchyma, particularly the frontal lobes. This never occurred in any of our patients because, although ventricular enlargement was sometimes present at the time of onset, its persistence was never such as to require shunting. The test performances did not correlate with any of the surgical variables (one vs more than one intervention or the presence of tumor residue). In our study, interhemispheric group had 7 cases and pterional group had 5 cases with hydrocephalus. However, none of them demonstrated pre-operative or post-operative behavior alteration. None of those patients required CSF diversion procedure too. Primary pathology was tackled at the first setting without any deleterious outcome. As a routine protocol, in all the patients operated by interhemispheric approach, we kept EVD in the third ventricle following tumor resection for 48 hours. Once EVD output is clear we removed EVD. Patients operated by Pterional Group did not require EVD.

LIMITATIONS OF THE STUDY

- Small sample size
- Variation in age and sex in both study group which may be confounding factor in our results.
- Short duration of follow up. However, all patients are still under follow up and we are considering them for neuropsychological evaluation during their follow ups to diagnose long term changes, if any.
- Both the study groups were not comparable with respect to the size and the extent of the lesion. Patients in the interhemispheric group had more extensive lesion with predominant third ventricle involvement, whereas patients in the pterional group had lesion with more lateral extension. However neuropsychological outcomes, both in preoperative as well as postoperative period, can be compared in both the approaches. Due to the small sample size, statistical significance could not be checked.
- No measures of behavioral or emotional self-regulation, such as the Behavior Rating Inventory of Executive Function, which was developed to assess everyday behavioral manifestations of executive control functions, were administered in this study unlike others (78–80). Neuropsychological and behavioral measures focus on different constructs within the executive function domain and often are not significantly correlated (81). It is possible that problems with behavioral or emotional self-regulation could occur in the absence of neuropsychological executive-functioning deficit in addition, it is possible that these patients had problems in everyday cognitive functioning that were not detected by the measures used. (82)

CONCLUSION

- The children treated for craniopharyngioma in our cohort did not present any neurological (except visual problems in some cases), cognitive or short-term memory deficits, except for a slight fluency and delayed recall in a few cases.
- Neither age nor the approach of surgical intervention, affected significantly their cognitive and neuropsychological functions.
- Overall, particular attention should be given to the depressive and fragile aspects of the personalities of these children, who may well need emotional support as they are on hormonal replacement treatment.
- In a microscopic era, our aim should be the gross total excision as it is not associated with any deterioration in neuropsychological and behavior outcome.
- Interhemispheric microscopic approach provides good access to the tumors located within the third ventricle and minimizes damage to the hypothalamus with minimal neuropsychological changes.

REFERENCES

1. Cushing H .Intracranial tumors. Notes upon a series of two thousand verified cases with surgical mortality percentages per- taining thereto. Thomas, Springfield,1932; 93–98.

2. Barkhoudarian G, Laws ER. Craniopharyngioma: history. Pituitary. 2012;16(1):1–8.

3. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007 Aug;114(2):97–109.

4. Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, Kristensen LØ, Astrup J, Jørgensen JO, et al. Incidence of craniopharyngioma in Denmark (n = 189) and estimated world incidence of craniopharyngioma in children and adults. Journal of Neuro-Oncology. 2011;104(3):755–63.

5. Cheng, M.K., 1982. Brain tumors in the People's Republic of China: a statistical review. Neurosurgery 10 (1), 16-21.

6. Haupt, R., Magnani, C., Pavanello, M., Caruso, S., Dama, E., Garre, M.L., Epidemiological aspects of cranio- pharyngioma. J. Pediatr. Endocrinol. Metab. 2006,19.

7. Lederman, G.S., Recht, A., Loeffler, J.S., Dubuisson, D., Kleefield, J., Schnitt, S.J., Craniopharyngioma in an elderly patient. Cancer 1987,60 (5), 1077-1080.,.

8. Arai T, Ohno K, Takada Y, Aoyagi M, Hirakawa K. Neonatal craniopharyngioma and inference of tumor inception time: case report and review of the literature. Surgical Neurology. 2003;60(3):254–9.

9. Izuora GI, Ikerionwu S, Saddeqi N, Iloeje SO. Childhood intracranial neoplasms Enugu, Nigeria. West Afr J Med. 1989 Sep;8(3):171–4.

10. Aghadiuno, P.U., Adeloye, A., Olumide, A.A., Nottidge, V.A., Intracranial neoplasms in children in Ibadan, Nigeria. Childs Nerv. Syst. 1985. 1 (1), 39-44.

11. Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. Neuro-Oncology. 2012;14(8):1070–8.

12. Vargas et al. Craniopharyngioma in siblings 1981 oct 16;246(16):1807-8.

13. Boch A-L, van Effenterre R, Kujas M. Craniopharyngiomas in Two Consanguineous Siblings: Case Report. Neurosurgery. 1997 Nov 1;41(5):1185–6.

14. Prabhu VC, Brown HG. The pathogenesis of craniopharyngiomas. Child's Nervous System. 2005;21(8–9):622–7.

15. Garre, M.L., Cama, A., Craniopharyngioma: modern concepts in pathogenesis and treatment. Curr. Opin. Pediatr.2007, 19.

16. M U Taruq, N nasir,A zubairPapilary craniopharyngioma. Papilary craniopharyngioma neurology india.2017 may,65(3):570-576.

17. Karavitaki N, Cudlip S, Adams CBT, Wass JAH. Craniopharyngiomas. Endocrine Reviews. 2006;27(4):371–97.

18. Szeifert, G.T., Sipos, L., Horvath, M., Sarker, M.H., Major, O., Salomvary, B., Czirjak, S., Balint, K., Slowik, F., Kolonics, L.,et al.,. Pathological characteristics of surgically removed craniopharyngiomas:analysis of 131 cases. Acta Neuro. ch. 1993,65(3):148-150

19. Pieter Pauw's observations from the 16th century ,Diabetes insipidus and blindness caused by a suprasellar tumor:. JAMA ,2008;279:48–50.

20. Zenker FA. Enorme Cystenbildung im Gehirn, vom Hir- nanhang ausgehend. Virchows Arch. 1857; 12:454–466.

21. Mott FW, Barratt JOW Three cases of tumour of the third ventricle. Arch Neurol Psychiatry.1899.1:417–440.

22. Saxer F. Ependymepithel, gliome und epithlische ge- schwülste des zentralen nervensystems. Ziegler‘s Beiträge. 1902;32:276.

23. Pascual JM, Rosdolsky M, Prieto R, Strauβ S, Winter E, Ulrich W. Jakob Erdheim (1874–1937): father of hypophyseal-duct tumors (craniopharyngiomas). Virchows Archiv. 2015;467(4):459–69.

24. Halstead AE (1910) Remarks on the operative treatment of 256 tumors of the hypophysis. Surg Gynecol Obstet 10:494–50225. Lindholm J. A century of pituitary surgery: Schloffer’s legacy. Neurosurgery. 2007 Oct;61(4):865–7; discussion 867-868.

25. Symon L, Sprinch W: radical excision of craniopharyngioma: results in 20 patients. J neurosurg 1994;62:174-181,

26. Laws jr, E.R. [Journal of Neurosurgery] Transsphenoidal microsurgery in the management of craniopharyngioma.1980.65-75

27. Gardner P.A, Gardner, P.A., Kassam, A.B., Snyderman, C.H., Carrau, R.L., Mintz, A.H., Grahovac, S., Stefko, S.Journal of Neurosurgery] Outcomes following endoscopic, expanded endonasal resection of suprasellar craniopharyngiomas_ a case series2012.56(8)545-548.

28. Gordy PD, Peet MM, Kahn EA The surgery of the craniopharyngiomas. J Neurosurg. 1949; 6:503–517.

29. Grant FC Surgical experience with tumors of the pituitary gland. J Am Med Assoc . 1948 ;136:668–671.

30. Mu¨ller R, Wohlfart G, Craniopharyngiomas. Acta Med Scand.1950; 138:121–138.

31. Treatment of craniopharyngiomas: the multimodality approach. Pediatr Neurosurg 1994;21(1):82–89.

32. Ingraham FD, Matson DD, McLAURIN RL. Cortisone and ACTH as an adjunct to the surgery of craniopharyngiomas. N Engl J Med. 1952 Apr 10;246(15):568–71.

33. Carpenter Rc, C.G., Frazier, Ch, The treatment of hypophyseal stalk tumors by evacuation and irradiation. AJRAm. J. Roentgenol. 1937; 38, 162-177.

34. Kiehna EN, Merchant TE. Radiation therapy for pediatric craniopharyngioma. Neurosurgical Focus. 2010 Apr 1;28(4):10-11.

35. Minniti G, Esposito V, Amichetti M, Maurizi Enrici R. The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngioma. Neurosurgical Review. 2009;32(2):125–32.

36. Hasegawa T, Kondziolka D, Hadjipanayis CG, Lunsford LD. Management of Cystic Craniopharyngiomas with Phosphorus-32 Intracavitary Irradiation. Neurosurgery. 2004;54(4):813–22.

37. Gopalan R, Dassoulas K, Rainey J, Sherman JH, Sheehan JP. Evaluation of the role of Gamma Knife surgery in the treatment of craniopharyngiomas.1998;25(2):135-138

38. Yeung, J.T., Pollack, I.F., Panigrahy, A., Jakacki, R.I., Pegylated interferon-α-2b for children with recurrent craniopharyngioma. jns ped 2012(5)65-70.

39. Duff JM, Meyer FB, Ilstrup DM, Laws ER, Schleck CD, Scheithauer BW. Long-term Outcomes for Surgically Resected Craniopharyngiomas. Neurosurgery. 2000;46(2):291–305.

40. Effenterre RV, Boch A-L. Craniopharyngioma in adults and children: a study of 122 surgical cases. Journal of Neurosurgery. 2002 Jul 1;97(1):3–11.

41. Lubuulwa J, Lei T. Pathological and Topographical Classification of Craniopharyngiomas: A Literature Review. Journal of Neurological Surgery Reports. 2016;77(03):121–7.

42. Puget S, Garnett M, Wray A, Grill J, Habrand J-L, Bodaert N, et al. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. J Neurosurg. 2007 Jan;106(1):3–12.

43. Yasargil, M.G., Curcic, M., Kis, M., Siegenthaler, G., Teddy, P.J., Roth, P., Total removal of craniopharyngiomas. Approaches and long-term results in 144 patients. J. Neurosurg. 1990;73 (1):3-11.

44. Pusey E, Kortman K, Flannigan B, Tsuruda J, Bradley WG. MR of craniopharyngiomas: tumour delineation and characterization. Am J Neuro Rad 1987;8:439-444

45. Banna M: Craniopharyngioma: based on 160 cases . .Br J Radiology 1976;49:206-223.

46. Curran JG, O'Connor E. Imaging of craniopharyngioma. Child's Nervous System. 2005;21(8–9):635–9.

47. Anderson A,greta N, Cridtopher N, . Neuro behaviour in crniopharyngioma. Pediatric neurosurgery 1997;26(5):255-260.

48. Cavazzuti V, Fischer EG, Welch K, Belli JA, Winston KR. Neurological and psychophysiological sequelae following different treatments of craniopharyngioma in children. Journal of Neurosurgery. 1983 Sep 1;59(3):409–17.

49. Bellhouse J, Holland A, Pickard J. Psychiatric, cognitive and behavioural outcomes following craniopharyngioma and pituitary adenoma surgery. British Journal of Neurosurgery. 2009;17(4):319–26.

50. Kent P. The Evolution of the Wechsler Memory Scale: A Selective Review. Applied Neuropsychology: Adult. 2013 Oct;20(4):277–91.

51. Bhattacharya B. Neuropsychological assessment: an overwiew, Bengal jr of psychiatry.2013;june,19:20-28

52. Tripathi R, Kumar JK, Bharath S, Marimuthu P, Varghese M. Clinical validity of NIMHANS neuropsychological battery for elderly: A preliminary report. Indian J Psychiatry. 2013;55(3):279–82.

53. Fanselow MS, Poulos AM. The Neuroscience of Mammalian Associative Learning. Annual Review of Psychology. 2005;56(1):207–34.

54. Ross T, Hanouskova E, Giarla K, Calhoun E, Tucker M. The reliability and validity of the self-ordered pointing task. Archives of Clinical Neuropsychology. 2007 May;22(4):449–58.

55. Wechsler D. Wechsler Intelligence Scale for Children. San Antonio, TX, US: Psychological Corporation; 1949. (Wechsler Intelligence Scale for Children).

56. Baskin DS, Wilson CB. Surgical management of craniopharyngiomas. A review of 74 cases. J Neurosurg. 1986 Jul;65(1):22–7.

57. Hoffman HJ, Silva MD, Humphreys RP, Drake JM, Smith ML, Blaser SI. Aggressive surgical management of craniopharyngiomas in children. Journal of Neurosurgery. 1992 Jan;76(1):47–52.

58. Woiciechowsky C, Vogel S, Lehmann R, Staudt J. Transcallosal Removal of Lesions Affecting the Third Ventricle: An Anatomic and Clinical Study Anatomical Report: 117. Neurosurgery. 1995 Jan;36(1):117–23.

59. Aglioti S, Tassinari G, Berlucchi G. Spatial Stimulus —Resonse Compatibility in Callosotomy Patients and Subjects with Callosal Agenesis. Neuroscience & Biobehavioral Reviews. 1996 Jan;20(4):623–9.

60. Pollmann S, Zaidel E. The role of the corpus callosum in visual orienting: importance of interhemispheric visual transfer. Neuropsychologia. 1998 Aug;36(8):763–74.

61. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. Journal of Neurosurgery. 1999 Feb;90(2):237–50.

62. Clopper R, Meyeriii W, Udvarhelyi G, Money J, Aarabi B, Mulvihill J, et al. Postsurgical IQ and behavioral data on twenty patients with a history of childhood craniopharyngioma. Psychoneuroendocrinology. 1977;2(4):365–72.

63. Katz EL. Late results of radical excision of craniopharyngiomas in children. Journal of Neurosurgery. 1975 Jan;42(1):86–90.

64. Weiss M, Sutton L, Marcial V, Fowble B, Packer R, Zimmerman R, et al. The role of radiation therapy in the management of childhood craniopharyngioma. International Journal of Radiation Oncology*Biology*Physics. 1989 Dec;17(6):1313–21.

65. Nauta WJH (1972) Neural associations of the frontal cortex. Acta Neurobiol Exp 32: 125–140

66. Galatzer A, Nofar E, Beit-Halachmi N, Aran O, Shalit M, Roitman A, et al. Intellectual and psychosocial functions of children, adolescents and young adults before and after operation for craniopharyngioma. Child Care Health Dev. 1981 Dec;7(6):307–16.

67. Riva D, Pantaleoni C, Devoti M, Saletti V, Nichelli F, Giorgi C. Late neuropsychological and behavioural outcome of children surgically treated for craniopharyngioma. Child's Nervous System. 1998 May 26;14(4–5):179–84.

68. Shiminski-Maher T. Patient/Family Preparation and Education for Complications and Late Sequelae of Craniopharyngiomas. Pediatr Neurosurg. 1994;21(1):114–9.

69. Konorski J, Teuber H-L, Zernicki B. THE FRONTAL GRANULAR CORTEX AND BEHAVIOR. 1980:6.

70. Vito JLD, Smith OA. Subcortical projections of the prefrontal lobe of the monkey. Journal of Comparative Neurology. 1964;123(3):413–23.

71. Nauta WJH, Some efferent connections of the prefrontal cortex in the monkey. In: Warren JM, Akert K. Symposium on the Frontal Granular Cortex and Behaviour. McGraw-Hill, New York San Francisco London,1964; 397–409

72. Asanowicz D, Marzecová A, Jaśkowski P, Wolski P. Hemispheric asymmetry in the efficiency of attentional networks. Brain and Cognition. 2012 Jul;79(2):117–28.

73. Posner M, Petersen S, Fox P, Raichle M. Localization of cognitive operations in the human brain. Science. 1988 Jun 17;240(4859):1627–31.

74. Posner MI, Petersen SE. The Attention System of the Human Brain. Annu Rev Neurosci. 1990 Mar;13(1):25–42.

75. Wright C, McAllister, II JP, Katz SD, Miller DW, Lovely TJ, Salotto AG, et al. Cytological and Cytoarchitectural Changes in the Feline Cerebral Cortex during Experimental Infantile Hydrocephalus. Pediatr Neurosurg. 1990;16(3):139–55.

76. Cristante F, Lis A, Sambin M. Statistica per psicologi. Giunti Editore; 2001. 488

77. Waber DP, Pomeroy SL, Chiverton AM, Kieran MW, Scott RM, Goumnerova LC, et al. Everyday Cognitive Function After Craniopharyngioma in Childhood. Pediatric Neurology. 2006 Jan 1;34(1):13–9.

78. Roth RM, Isquith PK, Gioia GA. Assessment of Executive Functioning Using the Behavior Rating Inventory of Executive Function (BRIEF). In: Goldstein S, Naglieri JA, editors. Handbook of Executive Functioning. New York, NY: Springer New York; 2014 ;Jul 10: 301–31.

79. Gioia GA, Isquith PK, Guy SC, Kenworthy L. TEST REVIEW Behavior Rating Inventory of Executive Function. Child Neuropsychology. 2000 Sep;6(3):235–8.

80. Anderson VA, Anderson P, Northam E, Jacobs R, Mikiewicz O. Relationships Between Cognitive and Behavioral Measures of Executive Function in Children With Brain Disease. Child Neuropsychology. 2002 Dec;8(4):231–40.

81. Waber DP, Pomeroy SL, Chiverton AM, Kieran MW, Scott RM, Goumnerova LC, et al. Everyday Cognitive Function After Craniopharyngioma in Childhood. Pediatric Neurology. 2006 Jan;34(1):13–9.

ANNEXURES

Sree Chitra Tirunal Institute for Medical Sciences & Technology

Proforma

Prospective observational study of outcomes of different transcranial approaches for craniopharyngiomas

General Instructions

Please fill in all the questions

Write Yes / No/NA wherever applicable

If the response is not known please write UK

If additional info is available please elaborate

Please use separate proforma for each admission

If admission is for a post operative complication please go to section E after completing the general information

Intraoperative illustrations will be appreciated

Annexure I

Hospital no:
Age
Sex
Date of admission:
Occupation:
Residence:
Handedness:

Clinical details-

Mode of presentation and Duration of symptoms:
Headache
Vomiting
Visual disturbance
Seizure
Sensorium changes
Electrolyte imbalance
Hormonal profile:
Comorbidities:

Examination finding:
GCS:
Built:
Vision:
Fundus:

Secondary sexual characteristics:
Systemic examination findings:

Pre operativeRadiology: MRI / CT.
Diagnosis
Size of lesion
Location
Extend
Hydrocephalus
Edema (grade)
Extent of lesion:

Neuropyschological assessment pre op:

Annexure II

Operative findings:
Date:
Approaches:
Position:
Craniotomy:
Characteristic odf lesion:

Extend of lesionectomy.
Use of hemostats – descriptive.
External ventricular drainage/ days/ volume/ microscopy.
Intra operative complications

Pathological diagnosis:

Annexure III:

Time of extubation
Duration of ventilator support:
Sensorium detail:
Complaints:
Post op complication and its management:
Clinical deficit:

Examination findings:
:

Post op radiology:
Date:
Infarcts- arterial - descriptive.
Hydrocephalus

Tumour removal- total/ near total (90%)/ Partial (70%)/ Less than 50%.
Venous infarcts/ haematoma – size, extend.
Odema.
Neuropsychological assessment:

Annexure IV
Hospital no:
Age
Sex
Date of admission:
Occupation:
Residence:
Handedness:

Clinical details-

Mode of presentation and Duration of symptoms:
Headache
Vomiting
Visual disturbance
Seizure
Sensorium changes
Electrolyte imbalance
Hormonal profile:
Comorbidities:

Examination finding:
GCS:
Built:
Vision:
Fundus:
Secondary sexual characteristics:
Systemic examination findings:

Neuropsychological assessment :

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/1157/DECEMBER-2017 01.01.2018

Dr. Mathew Abraham
Professor
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Mathew Abraham,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "PROSPECTIVE OBSERVATIONAL STUDY OF OUTCOMES OF DIFFERENT TRANSCRANIAL APPROACHES FOR CRANIOPHARYNGIOMAS (IEC/1157)" on 16th December, 2017.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 18.11.2017 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Patient Information Sheet and Consent Form in English and Malayalam*
6. *Proforma*
7. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 27.12.2017 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Patient Information Sheet and Consent Form(for patient and Children) in English and Malayalam*
6. *Proforma*
7. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 16th December, 2017 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
4.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
5	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
6.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
7.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
8.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
9.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
10.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
11.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

Page 2 of 2

Plagiarism Checker X Originality Report

Similarity Found: 7%

Date: Sunday, July 28, 2019
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Craniopharyngioma:

"**One would expect these congenital epithelial tumors to be capable of enucleation like Dermoid cysts elsewhere in the body, but they so definitely adhere to the adjacent structures neighboring on their place of origin, it is rarely possible to shell them out of their bed without the production of serious secondary symptoms. To be sure, one may occasionally succeed in stripping out a thin-walled cyst, and examples of this have been reported, but when the tumor is partly solidified, and calcareous, sad experience warns the surgeon to leave it pretty much alone." Harvey Cushing, 1932. (1)**

"Though this tumor is still an ominous disease, it seems fair to say, that the outlook has improved considerably." (2)

Introduction :

Craniopharyngiomas are rare CNS tumors defined by WHO as benign, partly cystic epithelial tumor of the sellar region presumably derived from Rathke's pouch epithelium. While it is benign in nature, the adhesion to surrounding structures may result in damage to sellar and parasellar tissues during surgery and hence it is called "Benign Tumor in a malignant location." (3)

Epidemiology:

Incidence: The data from 15 population-based craniopharyngioma studies, which included over 1000 cases, suggested the estimated incidence to be 1.34 patient per 1 million people. (4)