

**AN AUDIT OF ENDOCRINE DYSFUNCTION IN
CHILDREN WITH CRANIOPHARYNGIOMAS AT
RED CROSS CHILDREN'S HOSPITAL AND
GROOTE SCHUUR HOSPITAL FROM 1976 TO 2004**

AUTHOR:

**DR. ZAKIYYA OMARJEE
MBChB (UCT) FCPaed (SA)**

SUPERVISOR:

**DR. S.V. DELPORT
SENIOR SPECIALIST PAEDIATRIC ENDOCRINE
UNIT**

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DR. ZAKIYYA OMARJEE

SUPERVISOR : DR. S.V. DELPORT

*Department of Paediatric Endocrinology, School of Child and Adolescent health,
University of Cape Town*

ABSTRACT

Background

Craniopharyngiomas account for 6-10% of childhood brain tumours and are the third most common intracranial tumours of childhood. Despite their benign histological appearance, they are often associated with a poor outcome and have significant associated morbidity.

Aim

To analyse the data of children with craniopharyngiomas at Red Cross Children's Hospital and Groote Schuur Hospital from 1976 to 2004 with respect to age at presentation, presenting symptoms and preoperative and post operative endocrine dysfunction.

Patients and methods

The records of 45 children aged between 9 months and 13 years were reviewed. The majority of children in the study were aged between 5 and 10 years. There was a considerable delay in the diagnosis in most cases especially in areas outside of Cape Town. Pre operative tests prior to 2000 were incomplete but have improved since then. Twenty nine percent of our patients had a near total excision of the craniopharyngioma and 29% had partial excisions necessitating adjuvant radiotherapy. The endocrinological, neuro imaging and presenting symptoms were analysed and post operative tests were

reviewed.

Where possible neuropsychiatric assessments were accessed as well in order to assess long term neurocognitive deficits

Results.

The age of presentation of craniopharyngiomas in our group of patients was much younger than in other studies with the largest group of affected children being between 5 and 10 years of age. The most common presenting symptoms in this group were headaches (62%) and visual disturbances (57%).

Sixty four percent of the children had preoperative endocrine testing for pituitary dysfunction of which 59% were ACTH and TSH deficient and only 38% were growth hormone deficient.

After surgery multiple endocrinopathies were universal with 56% of children having pan hypopituitarism at follow up. There was no reversal of pre existing hormone deficits after surgery.

The management of craniopharyngiomas remains controversial. Twenty nine percent of our patients had a near total excision and 29 % had a partial excision combined with radiotherapy with a further 6 patients receiving intratumoral bleomycin for recurrences. Post operatively the majority of children were on replacement therapy but only 6 patients (14%) received human growth hormone or are receiving human growth hormone currently due to a lack of funds to provide human growth hormone for children with growth hormone deficiency.

Seventy percent of the children had central diabetes insipidus post operatively reflecting posterior pituitary damage.

Our overall survival rate from 1976 to 2004 was 91% with a mortality rate of 13%. Most of the deaths were attributed to recurrences of the craniopharyngioma and the complications of bleomycin treatment.

Conclusion

Craniopharyngiomas remain tumours associated with significant morbidity. Total excision of the tumour remains a favourable option but the proximity of the craniopharyngioma to the pituitary gland and optic tracts results in devastating sequelae. Although the medical and surgical management of craniopharyngiomas has improved, a significant number of patients had endocrine sequelae. The management of craniopharyngiomas in an African context compares favourably internationally but with limited resources especially with regard to growth hormone replacement, a large proportion of our children are not receiving optimal treatment.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

ACTH	adrenocorticotrophin hormone
GH	growth hormone
TSH	thyroid stimulating hormone
GnRH	gonadotrophin releasing hormone
FSH	follicular stimulating hormone
LH	luteinising hormone
D.I	diabetes insipidus
C.T	computerized tomography
M.R.I	magnetic resonance imaging
DDAVP	desmopressin

INTRODUCTION AND LITERATURE REVIEW

Craniopharyngioma is a parasellar and sellar tumour which constitutes 6 – 10% of all childhood brain tumours (2). They account for 80 – 90% of neoplasms arising in the pituitary area.

Craniopharyngioma is the third most common intracranial tumour of childhood and the most common paediatric tumour in the hypothalamus and pituitary region.

These tumours arise from squamous rest cells of the remnant of Rathke's pouch between the adenohypophysis and the neurohypophysis in the region of the pars tuberalis.

The origin of craniopharyngioma is undetermined although several theories exist (1).

One theory is that this tumour is another form of a midline congenital tumour not very different from an epidermoid cyst. Another theory suggests that they arise from inclusion of the dental anlage tissue. A third theory suggests that craniopharyngiomas, being remnants of the Rathke pouch, arise from squamous cell rests normally found at the junction of the pituitary stalk and pars distalis (1).

The two major pathological variants are adamantinomatous and papillary types.

The adamantinomatous type is so named because of its hardness which results from calcification.

This type is most common in children. The papillary type rarely has calcifications.

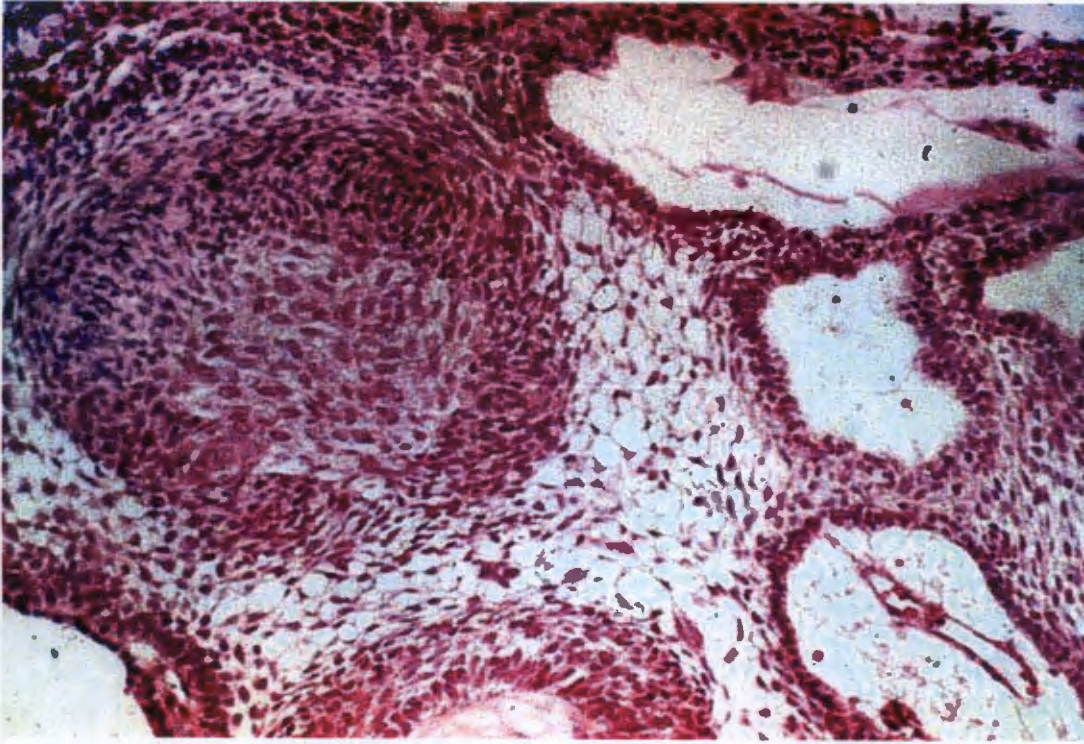


Figure 1 histological appearance of craniopharyngioma

Large tumours push the chiasm upward and displace the hypothalamus and third ventricle. Downward pressure compresses the anterior lobe of the pituitary gland and results in posterior lobe atrophy secondary to stalk damage.

The proximity to and subsequent pressure on vital structures of the brain , predispose the patients to many adverse sequelae depending on their location, size and growth potential. Despite their benign histological appearance, their prognosis may often be unfavourable and the optimal therapeutic approach remains controversial.

The pituitary gland is made up of an anterior and posterior lobe, each with a distinctive function.

The anterior pituitary produces growth hormone, thyroid stimulating hormone, adrenocorticotrophic hormone as well as follicular stimulating and luteinizing hormones whereas the posterior pituitary produces oxytocin and

anti diuretic hormones therefore any lesion of the pituitary will disrupt major hormonal pathways.(3)

The clinical presentation of craniopharyngiomas is not much different from that of other suprasellar tumours. Due to the proximity of the tumour to the hormone producing cells of the hypothalamus and pituitary gland there is significant endocrine dysfunction.

Clinical presentation of craniopharyngioma vary from dramatic symptoms of raised intracranial pressure with neurological disturbances such as headaches, vomiting and visual disturbances to manifestations of endocrine deficiency such as stunted growth and delayed puberty.

At diagnosis up to 80% of children will have endocrine dysfunction.

Growth hormone deficiency is common and occurs in 75% of children before the diagnosis of craniopharyngioma is made (11).

Two large studies showed that at presentation only 15% of the children on questioning had endocrine complaints but 50 – 68% are found to be short on examination (4).

Headaches are caused either by hydrocephalus with obstruction of CSF pathways at the Aqueduct of Sylvius or the Foramina of Munro or from stretching of the diaphragm sellae as the tumour grows. Visual deficits are caused by compression of the optic chiasm or other components of the optic apparatus such as the optic nerves by the suprasellar tumour growth. The most common visual disturbance is a bitemporal hemianopia (2). Such compression may produce optic nerve atrophy. Papilloedema resulting from raised intracranial pressure may also contribute to visual disturbances.

Other symptoms include behavioural and cognitive dysfunction as well as

seizures and gait disturbances (2).

Seventy percent of the tumours are located in the intrasellar and/or suprasellar region with only 20% being only suprasellar and 10% being purely intrasellar .

Craniopharyngiomas can occasionally grow into the third ventricle and cause hydrocephalus. The arterial supply is usually from the anterior cerebral arteries and anterior communicating arteries or from the internal carotid arteries and posterior communicating arteries (1).

A craniopharyngioma does not receive blood supply from the posterior circulation unless it is parasitized from the floor of the third ventricle. As these tumours enlarge they may elevate and infiltrate the optic chiasm as well as the hypothalamic region and as a result produce visual disturbances.

Craniopharyngiomas do not undergo malignant degeneration and are usually well defined. They are slow growing tumours and are usually about 3 – 4 centimetres in diameter and are usually cystic and may be multilobulated(1).

The ongoing debate on the treatment options with the least short and long term adverse effects poses further difficulties in establishing an effective management protocol.

No primary medical therapy exists for treatment of this tumour. The initial surgical decision concerns the approach with the goal of surgical intervention being gross total tumour removal with preservation of the optic apparatus and pituitary stalk.

The recent availability of high resolution magnetic resonance imaging has greatly improved the visualisation and radiological diagnosis of craniopharyngiomas. The neuroradiological diagnosis of a craniopharyngioma is based on the features of the lesion itself and its relation to surrounding structures.

The diagnosis of a craniopharyngioma is based on two characteristic features of the tumours –its cystic nature and the presence of calcification.



Figure 2 : MRI illustration of a craniopharyngioma

Though controversy surrounds the optimal management of craniopharyngiomas, most workers would recommend excision of the tumour as the definitive therapy. The management of these tumours is difficult and the approach may differ amongst different centres depending on factors such as experience of the medical team and the location of the tumour.

Depending on the location of the tumour either intrasellar or suprasellar , the surgical approach and type of excision differs.

If the predominant part of the tumour is intrasellar ,the transsphenoidal route is used.

Pterional craniotomy is the standard approach to suprasellar lesions as it allows good visualisation of the optic chiasm and pituitary stalk.

The aim of this study was to review the endocrine dysfunction in children with craniopharyngiomas pre operatively and post operatively in order to formulate a protocol for the future management of these children.

The objectives included an evaluation of the following parameters from information documented in the folders:

- 1. The presenting symptoms in the study patients in order to ascertain if the presentation was due to pituitary hormone deficiency or due to raised intracranial pressure.**

- 2. Identify specific endocrine abnormalities present at the time of diagnosis.**
- 3. . Document treatment modalities such as surgery, radiotherapy and chemotherapy implemented for craniopharyngiomas.**
- 4. Identify endocrinopathies before and after surgery.**
- 5. The hormonal replacement therapies patients were receiving.**

There is no published data in South Africa on craniopharyngiomas in children especially with regard to pituitary hormone deficiencies which are a major cause of morbidity and mortality.

METHODS

The medical records of 45 children aged between 9 months and 13 years (mean age 7 years) were reviewed from 1976 to 2004. There were 24 females and 21 males who had presented to Red Cross Children's Hospital and Groote Schuur Hospital with a diagnosis of craniopharyngioma.

The aim of this study was to investigate the presenting symptoms in our patients in order to ascertain if they were due to pituitary hormone deficiency or due to raised intracranial pressure, which endocrine abnormalities were present at the time of diagnosis, what treatment modalities the patients received and what post operative endocrinopathies were present after surgery and radiotherapy.

A retrospective review of patients folders and case records was conducted.

Ethics approval as well as permission from Groote Schuur Hospital and Red Cross

Hospital medical superintendents were obtained before patient folders were retrieved.

Because the study was a retrospective audit of folders, informed consent from the parents of the children with craniopharyngiomas was not obtained.

A data capture sheet (appendix A) was used to obtain the following information:

1. Age at presentation.
2. Age at diagnosis.
3. Presenting symptoms were divided into three categories : a) symptoms related to raised intracranial pressure b) symptoms related to anterior pituitary hormone deficiencies c) symptoms related to posterior pituitary hormone deficiencies d) other symptoms such as seizures, developmental delay, ataxia , loss of consciousness.
4. How the diagnosis of the craniopharyngioma was made – radiologically or histologically.
5. Preoperative endocrine tests.
6. Surgical and radiotherapy treatment modalities.

7. Incidence of recurrence of craniopharyngioma.

8. Post operative endocrine tests.

9. Hormonal therapy options.

Current protocols at Red Cross Hospital and Groote Schuur Hospital implemented by the Department of Neurosurgery and Paediatric Endocrinology requires that all children with craniopharyngioma have pre operative and post operative evaluation of the hypothalamic pituitary axis unless surgical intervention is urgent.

The results of tests conducted according to international guidelines were obtained from medical records at Red Cross Children's Hospital and Groote Schuur Hospital.

Both anterior and posterior pituitary function are tested by means of :

- 1) Metyrapone stimulation tests to assess the adrenocorticotrophin hormone axis.**
- 2) Clonidine stimulation and glucagons stimulation tests for growth hormone assays.**
- 3) Thyroid stimulating hormone levels and free thyroid hormone levels.**
- 4) Serum sodium and osmolality compared to urine osmolality.**

No formal water deprivation tests were done to confirm the diagnosis of diabetes insipidus.

Where possible these tests were done pre and post operatively but in most cases (29 of the 45 patients) the only pre operative assessments done were thyroid functions and electrolytes and serum osmolality.

Although there is no fixed protocol, followup imaging of the brain is done at regular intervals based on the clinical picture and at the discretion of the paediatric and neurosurgical teams. All the patients are followed up at the paediatric endocrine clinic and are admitted for relevant endocrine tests as they are required. They are also seen at a combined neurosurgical, radiotherapy and paediatric endocrine clinic where neuro imaging is reviewed and future endocrine and surgical procedures are planned.

Social worker involvement as well as occupational therapy is mandatory to ensure that school is continued in an appropriate environment. To date followup of children in this study has extended well into adulthood.

PATIENTS

The study population comprised 45 patients with craniopharyngiomas identified at Red Cross Children's Hospital and Groote Schuur Hospital.

Ages ranged between 9 months and 13 years with a mean age of 7 years. There were 24 females and 21 males in the study.

In most cases the diagnosis of craniopharyngioma was made based on radiological characteristics on CT head and magnetic resonance imaging of the brain and were confirmed histologically.

Imaging details were available for 40 patients. Skull xrays were done 7 patients and CT head scans were done on 31 patients. MRI brain scans were done on 10 patients of which 4 patients had had both CT head and MRI scans.

Histological diagnosis were available for 3 patients where the histology was confirmed before surgery was done.

ENDOCRINE EVALUATION

Preoperative endocrine evaluation of the hypothalamic pituitary axis in the 22 patients diagnosed with craniopharyngiomas prior to 1990 was limited.

Subsequently all children with craniopharyngiomas have a preoperative and a post operative evaluation of their pituitary hormone profile.

ANTERIOR PITUITARY TESTING

The evaluation of growth hormone deficiency was performed by the clonidine stimulation test which is standard practice in the paediatric endocrine department.

Growth hormone deficiency is defined as a peak growth hormone response of <10 ng/ml

following 0.1mg/metre squared dose of oral clonidine(11).

Other stimulation tests to assess growth hormone release include the arginine stimulation test and the insulin hypoglycemia test but due to the inavailability of intravenous arginine and the dangers associated with hypoglycemia in children , these tests are not used in our unit.

The adrenocorticotrophic axis was assessed by the response of ACTH and 11 deoxycortisol following the administration of metyrapone (30mg/kg given orally at 23h00 on the night before) . ACTH deficiency was defined by an ACTH response of <100pg/ml and 11 deoxycortisol response of <200nmol/l.

Thyroid hormone deficiency was defined as a low thyroid stimulating hormone level (TSH normal range 0.35 – 5.5 mIU /ml) with free thyroid hormone levels below the normal reference range (T4 11.5 – 22.7pmol/l and T3 3.5- 6.5 pmol/l) Ranke M.B

Diagnostics of endocrine function in children and adolescents.

Gonadotrophin deficiency was difficult to assess due to the unavailability of LHRH for stimulation testing and given that most of our patients were prepubertal , only 9 patients had LHRH stimulation tests once they were pubertal.

Gonadotrophin deficiency was defined as an inappropriately low FSH and LH responses following 2.5mcg/kg of GnRH given intravenously.

Diabetes insipidus was defined on the basis of urine output of 2500ml/metre squared body surface area/day in infants and 1500ml/metre squared body surface area/day in children with urine osmolality < 300 mOsm/kg and serum osmolality >298mOsm/kg.

The following information was obtained and presented in graph and table format.

1. Age distribution.
2. Presenting complaints.

- 3. Preoperative endocrine evaluation**
- 4. Number of Ventriculoperitoneal shunts and Omayo reservoirs.**
- 5. Surgical and radiotherapy options.**
- 6. Postoperative endocrine evaluation**

Heights and weights preoperatively and post operatively were inconsistently recorded and were therefore not used in the study although at followup all weights and heights are carefully plotted.

LITERATURE REVIEW

Similar studies have been conducted on a much more extensive basis internationally but the unique feature of this study is that there is no data within a South African context to highlight the extent of problems like growth hormone deficiency and the limited resources we have to provide growth hormone treatment to our patients.

Therefore literature reviews were conducted to assess how we could improve our test protocols and if our current practice was comparable to other centres.

Headaches	28 (62%)
Vomiting	10 (22%)
Visual disturbances	26 (57%)

SYMPTOMS RELATED TO PITUITARY DYSFUNCTION:

Polydipsia/polyuria	7 (15%)
Short stature	14 (31%)

NON SPECIFIC SYMPTOMS:

Weakness/hemiparesis	3 (6%)
Seizures	10 (22%)
Loss of independence	1 (2%)
Ataxia	4 (8%)
Deteriorating school work	3 (6%)
Loss of memory	2 (4%)
Weight gain	1 (2%)
Developmental delay	3 (6%)
Epistaxis	1 (2%)
Behavioural problems	1 (2%)
Decreased level of consciousness	2 (4%)

Karavitaki et al (5) found that headaches and visual disturbances such as diplopia and even blindness were the commonest pressure related symptoms in children.

Headaches occurred in 62% of the children as a presenting symptom and visual disturbances in 57 % of children which was detected either as presenting problem or on formal testing.

The commonest visual field defect was that of a bitemporal hemianopia due to optic chiasm compression by the craniopharyngioma.

Stretching of the diaphragm sellae by the enlarging tumour is one of the most likely causes of the headache and could also be as a result of the obstruction of the aqueduct of Sylvius and the Foramen of Munro causing hydrocephalus (1).

Growth hormone deficiency manifesting as short stature occurred in 31% of children at presentation largely due to destruction of the anterior pituitary gland by the craniopharyngioma. Although the other causes of short stature have to be considered, in the context of craniopharyngiomas it is assumed that preoperatively prior to growth hormone stimulation tests to confirm the diagnosis, that growth delay is most likely due to growth hormone deficiency.

Short stature was particularly a problem in the group where the diagnosis of the craniopharyngioma was delayed.

Seizures also occurred commonly as a presenting symptom in 22% of the group which could be due to raised intracranial pressure or due to the expansile nature of the tumour acting as an epileptogenic focus.

Most of the remaining presenting features were non specific and varied from fatigue and poor school performance to attention deficit hyperactivity disorder to account for regression in milestones and poor school performance.

Hydrocephalus was found in 23 patients necessitating urgent surgical intervention and the insertion of ventriculo peritoneal shunts.

DELAY IN DIAGNOSIS:

The delay in the diagnosis of craniopharyngioma from the time of presentation to the time of diagnosis varied very widely.

This time interval was ascertained from the history with regard to the duration of symptoms (particularly headaches) until the time the diagnosis was made.

On average there was a six month delay from presentation to diagnosis in most cases but

in 1 case there was a three year 8 month delay before the craniopharyngioma was diagnosed.

The delay could be attributed to a number of factors including the failure to recognise subtle symptoms and signs of raised intracranial pressure and endocrine dysfunction as well as the lack of neuro- imaging techniques such as CT heads and MRI scans in rural areas.

Inadequate growth monitoring particularly height measurements is also an important cause of the delay in diagnosis as a deterioration in growth velocity is probably the earliest sign of growth hormone deficiency. (6)

PREOPERATIVE ENDOCRINE DYSFUNCTION

Only 29 of the 45 children with craniopharyngiomas (64%) had preoperative pituitary hormone evaluation and it is assumed that this is because the remaining children required emergency management of raised intracranial pressure and hydrocephalus and were too ill to conduct preoperative tests on them. Preoperative endocrine tests on children with craniopharyngiomas were not routinely done at either Red Cross Hospital or Groote Schuur Hospital prior to 1992.

Table 3 : Results of Preoperative Pituitary Tests

HORMONAL ABNORMALITY	NUMBER OF PATIENTS (percentage)
GH deficiency	11 (38%)
TSH deficiency	19 (59%)
ACTH deficiency	19 (59%)
Diabetes insipidus	3 (10%)

GH = growth hormone

TSH = thyroid stimulating hormone

ACTH = adrenocorticotrophin hormone

PREOPERATIVE ENDOCRINOPATHIES

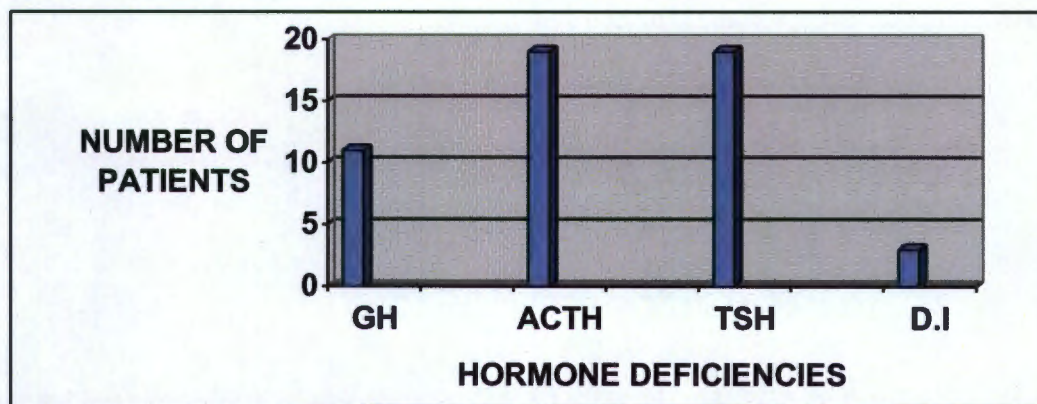


Figure 3 : Preoperative Pituitary Hormone Deficiencies

Unlike other studies (5) prolactin levels and FSH and LH levels were not measured in our patients . Hyperprolactinemia is largely due to pituitary stalk compression and with disruption of the hypothalamic pituitary axis and is more commonly associated with pituitary tumours in adults. Measuring prolactin levels in children with craniopharyngiomas is indicated to assess hypothalamic dysfunction and is an issue that should be addressed in the future.

Preoperatively all children found to have secondary hypothyroidism were supplemented with thyroxine orally at 100 mcg / metre squared a day , cortisol was replaced with dexamethasone pre and intra operatively and was then converted to hydrocortisone 8-12 mg/metre squared per day in 2 divided doses.

Desmopressin was commenced in children with central diabetes insipidus at 0.05 – 0.1ml (5 – 10mcg per dose) intra nasally.

VENTRICULOPERITONEAL SHUNTS AND OMAYA RESERVOIRS:

23 of our patients required ventriculoperitoneal shunts as emergency procedures in order to alleviate hydrocephalus.

Fifteen children particularly those with large cystic components to their craniopharyngioma had intratumoral Omayia reservoirs inserted in the event that

aspiration of the cyst was necessary. as well as for intratumoral brachytherapy to shrink the cyst.

NEURO IMAGING

Most of the craniopharyngiomas were diagnosed by imaging of the brain and then confirmed histologically intra operatively.

Table 4 : types of imaging techniques used

Skull x ray	7 (15%)
CT head	31 (69%)
MRI brain	9 (20 %)
Unknown	5 (11%)

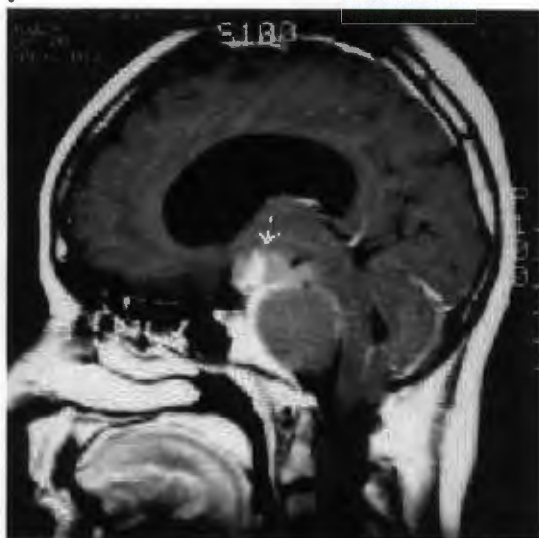


Figure 4:
MRI brain illustrating a craniopharyngioma

TREATMENT MODALITIES

Depending on the location of the tumour either intrasellar or suprasellar, the surgical approach and type of excision differs.

Pterional craniotomy is the standard approach to suprasellar lesions as it allows good visualisation of the optic tracts. Where possible total removal of the tumour is attempted

with preservation of the optic chiasm and pituitary stalk. If a subtotal resection is only possible adjunctive radiotherapy is used.

Table 5 : surgical modalities used to treat craniopharyngioma

PROCEDURE	NUMBER OF PATIENTS
Surgery only	13 (29%)
Surgery and radiotherapy	13 (29%)
Intratumoral radiotherapy	- yttrium 1 patient Bleomycin 6 patients
No surgery	1 patient
Inoperable	2 patients

In our population the transsphenoidal approach has not yet been attempted because of a lack of expertise and the size of the intra sella lesions makes this approach technically difficult in children. One patient has not been operated on because of the craniopharyngioma being too small for resection and the absence of any signs of raised intracranial pressure or visual impairment.

POST OPERATIVE PITUITARY HORMONE DEFICIENCY

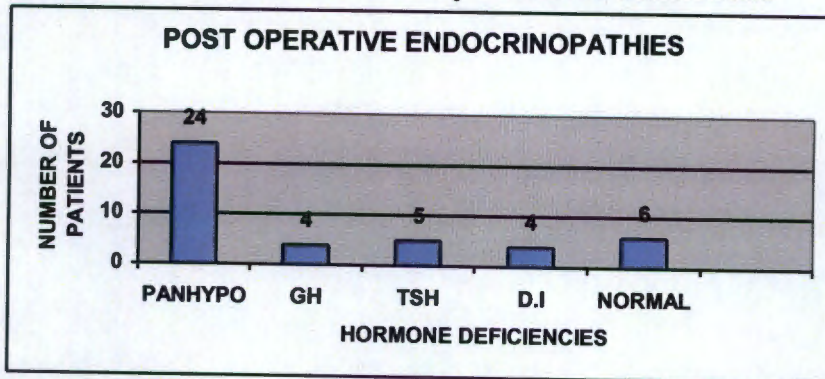
Significant morbidity and mortality is associated with craniopharyngioma surgery.

There was no reversal of pre existing pituitary hormone deficiencies after surgical intervention. Instead there was a more significant deficit in pituitary hormone dysfunction.

Table 6 : post operative endocrine dysfunction.

HORMONAL DEFICIENCY	NUMBER OF PATIENTS
	N=43 (100%)
panhypopituitarism	24 (56%)
GH and ACTH deficient only	4 (9 %)
TSH deficiency only	5 (11 %)
Diabetes insipidus only	4 (10%)
Normal	6 (14%)

Figure 5 : Post operative Pituitary Hormone deficiencies



Panhypo = ACTH/GH/TSH/FSH/LH deficiency and diabetes insipidus

GH = growth hormone

ACTH = adrenocorticotrophin hormone

TSH = thyroid stimulating hormone

D.I = diabetes insipidus

SURVIVAL

Number of deaths from 1976 to 2004 - 4

Cause of death :

1 due to recurrence of the craniopharyngioma with intralesional bleomycin extravasation

1 due to recurrence with an irresectable tumour

1 death due to severe hyponatremia and septic shock

1 death due to irresectable tumour at presentation

RECURRENCE OF CRANIOPHARYNGIOMA

There were 13 recurrences documented in the patient study. However in 20 patients recurrences were not documented.

BONE AGE:

Xrays of the left wrist and hand were taken in order to assess the bone age .

Bone age was scored according to Grulich and Pyle guidelines.

Only 24 of the 45 patients had bone ages done particularly in the last ten years of practice.

DISCUSSION

The study of endocrine dysfunction in children with craniopharyngiomas is not a unique study but the study in the context of a South African experience is, as it provided us with a useful way to analyse local children with craniopharyngiomas.

The limitations of this study being a folder review included :

Incomplete data recorded at the time of diagnosis particularly investigations for endocrine dysfunction.

Computer laboratory records only date back to 1995 therefore accessing old results was not possible.

Children were seen initially at Red Cross Childrens Hospital preoperatively and then transferred to Groote Schuur Hospital for post operative endocrine evaluation as well as radiotherapy and there was a significant loss in the details of preoperative endocrine investigations and details of the admission at Red Cross Hospital.

In most children with craniopharyngiomas, endocrine dysfunction is present long before the diagnosis of the tumour is established.

After treatment with surgery and/or irradiation endocrine problems become a major cause of morbidity and mortality.

AGE DISTRIBUTION

The distribution of age at presentation of the craniopharyngioma is shown in table 1 and Figure 2.

The largest group of children diagnosed with craniopharyngiomas were aged between 5 and 10 years which is much younger than in other studies (3) where the age of presentation was 11 years.

Our youngest patient was aged nine months at diagnosis.

There was no gender predilection of craniopharyngiomas. (Table 1)

PRESENTATION

The proximity to and subsequent pressure effects of craniopharyngiomas on the hypothalamus and pituitary, the visual pathways, the brain parenchyma and major blood vessels predispose patients to multiple clinical manifestations at the time of presentation. Neurological symptoms in children due to obstructive hydrocephalus and raised intracranial pressure are common in children whose cerebral tissue is particularly vulnerable.

The most frequent presenting features in our patients were headache (62%) , visual disturbances (57%), short stature (31%), vomiting (as a symptom of raised intracranial pressure) in 22% and seizures in 22% (Table 2).

Similarly in larger studies , headaches and visual disturbances were the commonest presenting symptoms in children , between 50 – 78% and 62 – 79% respectively.(20)

The signs and symptoms associated with raised intracranial pressure were identified in a significantly higher number of children than adults , which is in keeping with other reports suggesting that these features may be the commonest presenting symptom in children and should not be ignored (11).

Although previous studies have shown that only 7% of children with craniopharyngiomas present with short stature , in our study 31% were found to be short on presentation and had subnormal growth rates.

The majority of children who presented with seizures were diagnosed with craniopharyngioma following CT head as part of the investigation of the seizures.

Visual disturbances were a common presenting symptom and ranged from diplopia to complete blindness and visual field defects. The majority of children with craniopharyngiomas have bitemporal hemianopias but prolonged untreated raised intracranial pressure can cause optic atrophy and blindness.

Headaches in children with craniopharyngiomas was largely a symptom of raised intracranial pressure but in some studies was thought to be due to the stretching of the diaphragm sella by the enlarging tumour (1,6).

Among the hormone deficiencies growth hormone deficiency is the most common and is seen in approximately 75% of children with craniopharyngiomas(2). Growth failure or growth deceleration is a frequent cause for referral or investigation. (15).

After surgical treatment of craniopharyngiomas up to 90% of children show growth deceleration. Sorva (4) reported that in his study 19 patients had growth failure preceding the diagnosis of the craniopharyngioma by a mean of 4 years.

Similarly in the study population investigated here 31% (14 patients) were referred for investigation of short stature preceding the diagnosis of the craniopharyngioma.

Growth hormone secretion occurs in pulses and in between the pulses growth hormone levels may be undetectable therefore random growth hormone levels are of limited value. The diagnosis of growth hormone deficiency depends on provoking growth hormone secretion using physiological and pharmacological stimuli and if suspected should be tested pre operatively.(6)

Growth hormone treatment is recommended to facilitate catch up growth in growth hormone deficient patients shown to be free of the tumour after treatment. However the consequences of growth hormone therapy in patients with residual tumours is unclear as

there has been concern about recurrence of the tumour on growth hormone treatment.

Some centers begin growth hormone replacement within six months of surgery.

Two large studies have shown no increase in the risk of tumour recurrence in children receiving growth hormone following surgical removal of the craniopharyngioma (3).

The main problem facing the majority of children in developing countries including this patient population is the lack of funds to pay for human growth hormone replacement therapy and most of these children will not be privileged enough to receive this treatment purely because of the lack of finances in the State services.

DELAY IN DIAGNOSIS

There was a significant delay in the diagnosis of craniopharyngiomas in our study with a time interval ranging from six months to almost four years before the diagnosis of the craniopharyngioma was made in one case.

Headaches (as the most frequent presenting symptom in children) should be taken seriously and children should at least have fundoscopy to exclude papilloedema and in cases where visual defects are evident a CT head is indicated urgently.

It also appears that the delays in diagnosis occurred mainly in smaller towns outside of Cape Town where it is assumed that there is a lack of access to radiological facilities.

This delay in diagnosis needs to be addressed in the future and ways to improve our diagnostic time needs to be investigated.

In cases of less obvious symptoms such as poor school performance and fatigue as well as endocrine dysfunction, it is difficult to propose how to improve diagnostic tests in order to diagnose craniopharyngiomas in these children earlier. Here it is suggested that a high index of suspicion be maintained and that thorough physical examination with growth measurements be done on every child.

PRE OPERATIVE ENDOCRINE DYSFUNCTION

One of the aims of this study was to assess if endocrine dysfunction was present pre operatively in our patient cohort.

De Vile (12) suggested that although symptoms attributable to endocrine dysfunction were uncommon as the presenting complaint the majority of patients had symptoms to suggest an endocrinopathy at diagnosis.

The available data for pre operative endocrine status in children with craniopharyngiomas

suggest that hypothalamic pituitary dysfunction is present in 80-90% of subjects (7).

In our study pre operative endocrine tests were incomplete as only 29 of the 45 children (64%) had had preoperative pituitary hormone investigations.

Possible reasons for this include the fact that on admission children with newly diagnosed craniopharyngiomas were admitted by the neurosurgical team before the endocrinologists were aware of the patients and the opportunity to do pre operative tests were missed.

Further more since hydrocephalus and raised intracranial pressure is a common presenting feature in children, it is likely that these children were taken to theatre for emergency ventriculo peritoneal shunts and were too ill to conduct any blood tests on.

All children with craniopharyngiomas are however commenced on dexamethasone preoperatively and post operatively are monitored closely for central diabetes insipidus.

The incidence of other pituitary hormone deficits before surgery has been documented as 75% for growth hormone deficiency (GH)

25% for thyroid stimulating hormone (TSH) and adrenocorticotrophin hormone (ACTH) deficiency

9-17% for anti diuretic hormone deficiency (ADH)

40% for gonadotrophin hormone (GnRH) deficiency (5)

Our study shows a higher incidence of ACTH and TSH deficiency rather than GH deficiency but this is most likely because most children have routine thyroid function tests, serum osmolality and electrolytes preoperatively and are not subjected to provocative growth hormone testing prior to surgery..

Halac (6) suggests that IGF1 and IGF binding protein 3 (IGF BP3) assays be done in conjunction with a bone age and if the bone age was delayed with both IGF-1 and IGF-

BP3 levels low then the patient was growth hormone deficient and did not require provocative tests to prove growth hormone deficiency.

If the IGF1 was normal then growth hormone stimulation tests were indicated.

Most of our patients were prepubertal at the time of diagnosis and did not have LHRH stimulation tests preoperatively.

ACTH deficient children were treated with hydrocortisone at 8-12mg / metre squared per day in two divided doses with the bigger dose being taken in the morning.

ACTH deficiency may be very subtle but at times of stress can lead to hypotension and death. A diagnosis of ACTH deficiency can be made by finding sub normal cortisol levels and low ACTH levels.

ACTH deficiency was reported in 25-71% of children with craniopharyngiomas preoperatively (4).

Thyroxine replacement was commenced on children with secondary hypothyroidism who had a low TSH with a low free thyroid hormone level (FT4).

At diagnosis 10% of our patients had ADH deficiency which has been found to be present in up to 38% of children with craniopharyngiomas at the time of diagnosis(6).

Evaluation of the fluid and electrolyte status of craniopharyngioma patients is important since appropriate treatment of diabetes insipidus can minimize morbidity and mortality.

Determination of urine specific gravity, urine and serum osmolality and serum electrolytes is part of the initial laboratory workup.

The diagnosis of central diabetes insipidus is confirmed by the inability to concentrate urine despite elevation of plasma osmolality and is easily treated.

The most common presenting symptom of craniopharyngiomas in adults is

gonadotrophin deficiency. Most of our patients are pre pubertal therefore FSH and LH levels are not routinely measured. Levels of oestradiol in girls and testosterone in boys are within the pre pubertal range and these patients are commenced on hormonal replacement treatment at an appropriate age for pubertal development.

PROLACTIN

Increased prolactin levels were noted in 8-50% of children with craniopharyngiomas pre operatively (4).

Hyperprolactinemia results from disturbed secretion the prolactin inhibiting factor due to hypothalamic damage.

Prolactin levels are not measured routinely in our patients and will be proposed as a recommended test of hypothalamic function in the future (see conclusion and proposals).

VP SHUNTS AND OMAVA RESERVOIRS

The ideal approach to a craniopharyngioma is a total resection, owing to the fact that a partial resection will later lead to a recurrence. However because a total excision is not always possible and often results in major deficits such as hypothalamic dysfunction a palliative procedure in combination with radiotherapy or chemotherapy is preferred.

Unilateral or bilateral VP shunts were required in 23 of our patients (54%) as emergency procedures to alleviate hydrocephalus .

In 1985 Takahashi demonstrated a reduction in the cystic portion of the craniopharyngioma after direct injection of bleomycin into the cyst (34).

The rationale for intramural bleomycin injection as an adjuvant therapy for craniopharyngiomas are because most tumours are associated with a cyst, it is an epithelial tumour and although ideally treatment of a craniopharyngioma is a complete excision, total excision is not possible in many cases especially where the tumour is located adjacent to vital structures.

In our study , 6 of our patients received intratumoral bleomycin particularly in children who had had a recurrence or were too young for external beam irradiation. Bleomycin acts by inhibiting DNA synthesis and also inhibits the synthesis of proteins.(31) It was found to decrease secretion of cystic fluid and cause tumour cells to degenerate.(31)

Intratumoral bleomycin is recommended when total excision of a cystic craniopharyngioma is not possible especially in young patients.

The treatment of craniopharyngiomas remains controversial which reflects the heterogeneity of these tumours and the difficulty in management. Total tumour excision yields the best outcome but this is not always possible. There are several operative

approaches which take into account visual field defects and lateralisation of the mass.

29% of our patients had surgery only with a near total excision of the craniopharyngioma.

In a further 29% , only subtotal resections were possible and these children then have had adjuvant radiotherapy.

Despite its benign nature craniopharyngiomas often cause neurological and endocrinological impairment. Most neurosurgeons believe that total excision is the only reliable approach to prevent recurrence. However even after total resection, the recurrence rate is still high and the severity of endocrine dysfunction tends to correlate with the extent of the resection.

Radiotherapy may be effective in preventing the recurrence of the tumour when total resection is not possible. However because of the location of the craniopharyngioma adjacent to the hypothalamus and pituitary gland, radiotherapy should be considered carefully especially in young children.

One of the study patients had a small intrasellar craniopharyngioma which has not caused any pressure effects or visual deterioration and has therefore not been operated on yet. Transsphenoidal resection of the tumour would be ideal in this patient but due to technical difficulties such as the size of the sella turcica being too small in children, this procedure was not undertaken.

POST OPERATIVE HORMONE DEFICIENCY

Recovery of pre operative deficits following craniopharyngioma surgery is rare. Damage to the hypothalamic pituitary system exerted by the hydrocephalus or the tumour itself is permanent. In this series as well as in other reports (1,2,4,11,34) craniopharyngiomas were associated with a high rate of long term endocrine morbidity.

The deterioration of endocrinological function may be attributed to the damage by the tumour and its recurrences, the surgical interventions as well as the effects of radiotherapy.

The majority of the study patients (56%) had panhypopituitarism post operatively reflecting both anterior and posterior pituitary damage.

Interestingly enough 13% of patients had no pituitary hormone deficits in the short term and these were the children that had had surgery only without radiotherapy.

This further supports the theory that the surgical approach used can greatly influence the severity of endocrine dysfunction. In some studies it has been suggested that the transsphenoidal approach is the best approach to preserve pituitary function (5).

The attempt to preserve the pituitary stalk is a time consuming process but is rewarded with improved endocrinological results. It has been reported in the literature that the degree of post op endocrine deficiency depends on the extent of the tumour removal (5).

This study did not specifically look at which groups of children had endocrine dysfunction in relation to the type of surgical approach they had been subjected to as it would help explain the variability in endocrine dysfunction from panhypopituitarism to normal pituitary function.

External beam radiotherapy carries a high risk of delayed endocrine deficiency of anterior pituitary functions and endocrinological function gradually deteriorates over time. The effect depends on the radiation dose and because of the delayed onset of endocrine dysfunction all children who have had radiotherapy need to be monitored for growth deceleration, hypothyroidism and cortisol deficiency.

The rate of diabetes insipidus is high post surgery and in some children tends to be transient.

Sixty five percent of the study patients had diabetes insipidus post surgery which is similar to other studies (5).

In this series the unique phenomenon of growth without growth hormone has also been documented in two of our patients.

Excessive weight gain is one of the most distressing manifestations of hypothalamic injury following craniopharyngioma surgery and has been thought to be the reason for growth despite being growth hormone deficient.

Two distinct mechanisms (30) of hypothalamic obesity are now recognized. Injury to the ventromedial nuclei results in a complex of autonomic disturbances whereby increased parasympathetic and reduced sympathetic activity lead to hyperinsulinemia and decreased thermogenesis. The second mechanism involves injury to the paraventricular nuclei whereby hyperphagia is a direct result and is a sufficient cause of excessive growth.

Rapid weight gain is a sensitive indicator of hypothalamic dysfunction and makes surgical decisions to avoid further hypothalamic damage of paramount importance.



Figure 7 : MRI image of craniopharyngioma

NEUROIMAGING

The rationale behind imaging of the brain is to define as accurately as is possible the altered geography and peculiar character of complex neoplasms.

The imaging of craniopharyngiomas may include skull xrays, computerized tomography (CT) scans or magnetic resonance imaging scans (MRI) to define regional anatomy.

Although only 15% of the study patients had skull xrays , a skull xray provides the most accurate depiction of the sella and calcification associated with craniopharyngiomas.

The majority of patients (69%) had CT scans and in some cases both CT heads and MRI brains were done to define the lesion. Contrast CT scan will enhance the solid portion of the tumour and often the cyst capsule as well.

MRI is best done to define the brain- mass interface.

Neuro imaging provides an excellent road map if done correctly. Without adequate preoperative imaging , neurosurgical intervention is compromised. Where possible an MRI of the brain should be done as well.

SURVIVAL

Craniopharyngiomas are associated with decreased survival (3,5,6,13,18) . The long term morbidity of craniopharyngiomas is associated with damage to critical neuronal structures by the primary or recurrent tumour and/or with the adverse effects of the therapeutic interventions. The assessment of the treatment option with the least long term morbidity is difficult as recurrences and subsequent therapeutic interventions contribute to the final outcome.

The overall survival rate for our patient population is 91% which correlates with other bigger studies as well.(5)

Karavitaki et al (5) demonstrates an overall cumulative probability of survival of 91% at 5 years and 90% at 10 years following diagnosis. Ten year survival rates were better after complete removal of the tumour and in the group that had had a partial removal of the tumour followed by radiotherapy.

An accidental extravasation of bleomycin in one of our children underlines the potential hazards of intratumoral chemotherapy.

The study demonstrated a favourable outcome despite recurrences with only one death attributable to tumour recurrence.

Long term morbidity of craniopharyngiomas is associated with damage to critical neuronal structures by the primary or recurrent tumour.

Inadequate data in the bedletters precluded the collection of data regarding neuropsychiatric and neurocognitive evaluation..

Karavitaki (5) also showed that a significant number of patients had permanent motor deficits, epilepsy, and psychological disorders necessitating treatment .Although there is no doubt that cognitive impairment occurs in the developing brain, the modern techniques with reduction of the volume of the exposed normal tissue and optimizing the irradiation dose has contributed to minimizing neurocognitive deficits.

Another component of this study which we were unable to complete is that of the comparison of premorbid weights with post operative weight gain as a reflection of hyperphagia and the severity of hypothalamic dysfunction.

The importance of this must be emphasized especially with regard to the possibility of developing type 2 diabetes and insulin resistance associated with obesity as well as hyperlipidemias and the devastating consequences thereof.

Pereira (10) in a study at Leiden University also confirmed the long term adverse cardiovascular, neurological and psychosocial morbidity after treatment of a craniopharyngioma.. As shown in this study , survival post craniopharyngioma treatment is favourable but the long term prevalence of hypopituitarism was high (89%) and the long term sequelae of cardiovascular complications needs to be closely screened for especially in post pubertal individuals where oestrogen replacement in females especially needs to be actively implemented.

CONCLUSION

Within the constraints of a retrospective folder audit , the presenting symptoms and preoperative and post operative pituitary hormone deficits in 45 children diagnosed with craniopharyngiomas from 1976 to November 2004 were assessed. Although this information is widely available in large international studies, it is important that the the morbidity associated with craniopharyngiomas in children in an African context where access to MRI scans is limited and treatment options curtailed by financial constraints, was documented.

The shortcomings of this study include the fact that being a retrospective folder audit access to information was limited by incomplete notes as well as the fact that most patients were diagnosed at Red Cross Children's Hospital and then transferred to Groote Schuur Hospital for endocrine workup or radiotherapy with incomplete notes and inadequate referral letters.

The endocrine team prior to 2000 were not timeously informed of the patients and the opportunity to conduct preoperative tests was lost. Moreover the laboratory computer systems since 2001 have been upgraded and all old laboratory results prior to this time are not accessible thereby making it difficult to check up on old data and laboratory results.

Various pharmacological agents can influence the tests conducted to assess growth hormone and adrenocorticotrophin hormone. The use of high dose glucocorticoid steroids can cause generalized suppression of growth hormone, ACTH, thyroid hormone and prolactin. Phenytoin and carbamazepine can also interfere with thyroid function and give falsely reduced levels of TSH and thyroxine, particularly when anti epileptic agents are

used to treat seizures at presentation.

The interpretation of our test results needs to take these factors into consideration .

Adrenal insufficiency may mask the signs and symptoms of central diabetes insipidus.

The absence of glucocorticoids can ameliorate polyuria and increase urine osmolality of patients with untreated diabetes insipidus. Therefore all test results need to be interpreted in the context of the patient and the medication they are receiving.

This study confirmed the widely accepted view that craniopharyngiomas although benign in histological appearance are often associated with unfavourable and occasionally deleterious sequelae.

It also showed that presenting complaints in children usually relate to raised intracranial pressure effects but evidence of hypothalamic pituitary dysfunction, in particular short stature was often present at the time of diagnosis.

Preoperative endocrine evaluation although not always complete has been routine practice in the last 5 years.

Compared to other studies the majority of our patients were aged between 5 – 10 years.

Of major concern is that the delay in diagnosis of the craniopharyngioma was significant and in order to prevent this from occurring all health care practitioners in the clinics or in general practice are urged to take a detailed history particularly with regard to headaches and to plot weight and especially height at each visit as growth deficiency is probably the most subtle sign of growth hormone deficits.

In this review, hypothyroidism and adrenal insufficiency secondary to ACTH deficiency followed by growth hormone deficiency were common at diagnosis. Features of diabetes insipidus were uncommon at diagnosis but very common post operatively.

The long term consequences of the craniopharyngioma and its treatment although improved during the last two decades still remains bleak.

Despite the fact that the majority of patients in this study had panhypopituitarism post operatively , only a minority received growth hormone treatment due to financial constraints.

As indicated before growth hormone is not only required for linear growth but also assists in somatic growth and acquisition of bone matrix. Therefore the inability to provide this treatment has had significant consequences for our patients.

Apart from the type of treatment, the identification of clinical and imaging parameters to provide prognostic indicators is also difficult and is an area that needs further investigation.

The establishment of prognostic factors at a pathological level and the impact of new surgical approaches remains to be determined.

Even if hormone levels are adequate in the short term, .after surgical resection or radiotherapy , hormonal deficiencies may develop over years and patients need to be monitored closely.

ECOMMENDATIONS

Following the review of our patient cohort the following recommendations have been suggested in order to optimize management of our children with craniopharyngiomas:

1. Headaches and visual disturbances in children need to be investigated - fundoscopy can be conducted at the initial examination-
2. Adequate growth monitoring with regular height measurements can indicate growth delay before the effects of raised intracranial pressure are manifest. Endocrinologists have an advocacy role to promote improved growth monitoring to facilitate early referral and diagnosis
3. Essential preoperative endocrine evaluation includes testing for and treatment of ACTH adrenal insufficiency , assessment of salt and water balance and thyroid function
4. Prolactin levels should be measured postoperatively as an indicator of the disruption of the hypothalamic pituitary axis
5. Bone age xrays in combination with IGF -1 levels may help define the presence of growth hormone deficiency where growth hormone stimulation tests are contraindicated
6. Post surgery and radiotherapy more extensive anterior and pituitary testing needs to be conducted including re evaluation of the ACTH adrenal axis, growth hormone release, thyroid functions and electrolytes and osmolality ideally in a controlled environment with the appropriate stimulation tests
7. Regular followup at a multidisciplinary clinic to monitor for:-
 - Recurrences of the craniopharyngioma
 - Visual deficits
 - Growth parameters including excessive weight gain as an indicator of hypothalamic damage

- Monitoring response to hormonal treatment especially hydrocortisone , thyroxine and DDAVP (desmopressin).
- Implementing oestrogen and testosterone replacement therapy timeously
- Bi annual lipid and glucose monitoring
- Establishment of either a national growth hormone budget or acquisition of non governmental agencies to finance growth hormone replacement therapy
- Comprehensive neuropsychiatric and cognitive followup for appropriate school placement

**ALGORITHM FOR PRE OPERATIVE EVALUATION
OF CHILDREN WITH CRANIOPHARYNGIOMAS**

Height and weight measurement

Ophthalmological assessment

CT head / MRI brain

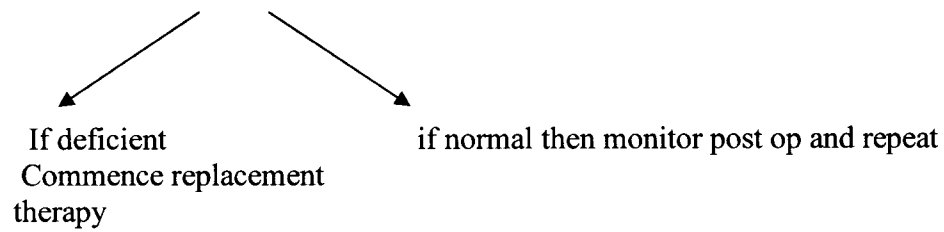
Bone age

Blood investigations : 8a.m cortisol

TSH

urine and serum electrolytes and osmolality

IGF1



ALGORITHM FOR POSTOPERATIVE EVALUATION OF CHILDREN WITH CRANIOPHARYNGIOMAS

SHORT TERM

Confirm histology

History to document diabetes insipidus, visual deterioration and raised intracranial pressure

Height and weight measurement including body mass index and body surface area

Anterior pituitary tests: TSH

 Metyrapone stimulation test

 Growth hormone stimulation test

 Prolactin

Posterior pituitary tests urine and serum osmolality and electrolytes if indicated water deprivation test

LONG TERM

Height and weight at each visit

Complete neurological examination

Pubertal staging

6 monthly thyroid function screen

Annual ophthalmology screen

Annual bone age xray

6 monthly fasting lipid profile and glucose monitoring

CT head / MRI brain with any suggestion of recurrence or if the craniopharyngioma was only partially resected

Adjust medication doses according to changes in height and weight

Neuropsychiatric assessment

School placement

Social worker for child dependency grant and emotional support

Radiotherapy and neurosurgical input at least every 6 months or as problems arise (team work)

FOR THE FUTURE

Formulate a list of prognostic factors for craniopharyngiomas based on the Red Cross

experience such as :

Age at diagnosis

Histology

Size of the tumour and involvement of adjacent neural structures

Preoperative endocrine deficits

Type of surgical intervention

Post operative endocrine deficits

Severity of neuropsychiatric deficits

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CONTACT DETAILS:

Dr Zakiyya Omarjee
P.O.BOX 38434
Gatesville
Cape Town
7766

Telephone : 0926461 229786
09264813007586 (cell)

Dr. S.V. Delport
Ward G25 Groote Schuur Hospital
Paediatric Endocrine Unit
021-404 3380
0832709305

Appendix A

CRANIOPHARYNGIOMA AUDIT DATA CAPTURE SHEET

NAME

FOLDER NUMBER

DATE OF BIRTH

AGE AT PRESENTATION

AGE AT DIAGNOSIS

PRESENTING SYMPTOMS:

HEADACHE

VISUAL DISTURBANCES

SHORT STATURE

POLYURIA/POLYDIPSIA

OTHER

DIAGNOSIS-RADIOLOGICAL

HISTOLOGICAL

WEIGHT AT PRESENTATION

HEIGHT AT PRESENTATION

PRE OPERATIVE ENDOCRINE TESTS

TSH

ACTH

GH

DIABETES INSIPIDUS SCREEN

TREATMENT

SURGERY resection –total

Subtotal

Partial

Shunts Y/N

Omayya reservoir Y/N

If yes intralesional yttrium /bleomycin

RADIOTHERAPY Y/N

**POST OPERATIVE ENDOCRINE ASSESSMENT
ANTERIOR PITUITARY FUNCTION**

TSH

ACTH

GH

FSH/LH

POSTERIOR PITUITARY FUNCTION

Serum Na

Serum osmolality

Urine osmolality

POST OP WT AT 1 YEAR FOLLOW UP

POST OP HEIGHT AT 1 YEAR FOLLOWUP

ENDOCRINE TREATMENT MODALITIES

Thyroid hormone (eltroxin)

Hydrocortisone

Growth hormone

Oestrogen/testosterone

DDAVP

NEUROPSYCHIATRIC ASSESSMENT

LEVEL OF FUNCTION

RECURRENCE Y/N