POSTERIOR FOSSA TUMOURS IN CHILDREN AT PARIRENYATWA HOSPITAL

THIS RESEARCH STUDY IS SUBMITTED IN PARTIAL FULFILMENT OF THE DEGREE IN MASTERS OF MEDICINE (NSG)

DEPARTMENT OF SURGERY, COLLEGE OF HEALTH SCIENCES, UNIVERSITY OF ZIMBABWE

2015

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Dedication

To my wife, Linda

Your unending support has made this project possible.
Declaration

I hereby declare that this submission is my own work and that to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of a university or other institute of higher learning, except where due acknowledgement is made.

………………………………

DR NYARARAI TOGAREPI
ACKNOWLEDGEMENTS

1. Professor K.K.N Kalangu – A supervisor who has worked tirelessly guiding this project.

2. Mr Musara – For selflessly taking time to give positive contributions.

3. Mr Mandozana – For statistical support.

4. Mr M. Muziringa – Library support and referencing assistance

5. NECTAR – For financing the project.

6. Department of surgery – Approval of study.

7. Parirenyatwa hospital – For permissions to carry our study within ward A2.

8. Medical Research Council of Zimbabwe – For ethical guidance.

9. Joint research and ethical committee – For assessment of the proposal and subsequent approval.
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List of abbreviations

1. CNS – Central nervous system
2. CCNU – 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea
3. CT – Computerized tomography
4. EPN-PFA – Ependymoma balanced genome(anaplastic)
5. EPN-PFB – Ependymoma chromosomal instability(anaplastic)
6. F – Female
7. Gy – Grays
8. HIV – Human immunodeficiency virus
9. ICU – Intensive care Unit
10. IQR – Interquartile range
11. KIAA1549:BRAF
12. M – Male
13. MEK – Mitogen extracellular kinase
14. MRCZ – Medical research council of Zimbabwe
15. MYC – Myelocytomatosis viral oncogene oncogene homologue
16. ‘O’ level – Ordinary Level
17. SD – Standard deviation
18. TP53- Tumour protein 53

19. SHH – Sonic Hedgehog

20. VP – Ventriculoperitoneal

21. WHO – World health organization

22. WNT – Wingless type MMTV(mouse mammary tumour virus) integration site member

23. YR-Year
Abstract

**Background:** It is important to know the epidemiology of posterior fossa tumors in children. Groups at risk can then be identified and followed up with the aim of reducing late presentation and improving outcome. However larger, long term studies are needed to accurately achieve this.

**Objectives:** The aim was to describe the effect of demographics, social background and HIV on the occurrence of posterior fossa tumors.

**Design:** Prospective Cross sectional study of children treated for posterior fossa tumors at the Neurosurgical unit of Parirenyatwa referral hospital.

**Setting:** Neurosurgery unit, Parirenyatwa teaching and referral hospital.

**Materials and methods:** A total of 32 children admitted with imaging demonstrating a posterior fossa tumor were included after the parents gave consent for their children to participate in the study. No patients were excluded from the study. All patients were also tested for HIV using the antibody tests. Data was collected by administering a questionnaire.

**Results:** Most cases came from Manicaland province with mean age of the patients being 6.7(SD) years and age ranging from 2 – 12 years. Median time to presentation from symptom onset was 3.5[2 - 6] months. Most patients were of poor socio economic status. A total of 7(21.7%) were HIV positive.

**Conclusion:** Posterior fossa tumors at Parirenyatwa hospital occur more commonly in low income families from Manicaland. There was a higher HIV rate in the study patients compared to the pediatric population. The sample size was however too small to demonstrate a statistically significant correlation between HIV and posterior fossae tumor occurrence.

**Keywords:** posterior fossa tumor, epidemiology, socio-demographics, pediatric brain tumors, HIV
Chapter 1

1. Introduction

The posterior fossa is a small region of cranium bordered on all sides by bone and limited superiorly by the tentorium with the foramen magnum inferiorly. The brain stem, cerebellum, and fourth ventricle are the main contents in this region of cranium. Expansion of a mass in this area occurs at the expense of the normal structures in the region and may result in brain stem or cerebellar dysfunction, often associated with obstruction of the fourth ventricle and hydrocephalus. Although many different tumor types may arise in the posterior fossa and affect the brain stem, cerebellum, and fourth ventricle, the most frequent are medulloblastomas, ependymoma, cerebellar astrocytoma, brain stem gliomas and less frequently higher grade cerebellar glial tumors (1). There are no local studies done to determine the epidemiology of posterior fossa tumors in children presenting at Parirenyatwa hospital, the only public hospital where major neurosurgical interventions are carried out in Zimbabwe. The purpose of the study was therefore mainly to describe the epidemiology of these tumors including age distribution and patients’ places of origin in Zimbabwe. The methodology included a descriptive cross sectional study design in a study population drawn from neurosurgical patients below the age of 12. These were patients admitted in the neuropediatric unit and selected according to the set exclusion and inclusion criteria before being followed up to the time of discharge. Patients were recruited over a period of 20 months and questionnaires administered to a sample size of 32. All guardians agreed to consent with no orders of cancellation of consent given at any time during the study.
1.1 Problem statement
The description of demographics, social background, HIV and their effect on the occurrence of posterior fossa tumors has not been done in Zimbabwe.

1.2 Justification of study
Prompt diagnosis, timeous, appropriate and specific treatment of posterior fossa tumors have been shown to be important factors in achieving a favorable outcome(2). The social backgrounds, demographic and HIV associations have not been widely researched on in Zimbabwe. This paucity of these data at Parirenyatwa hospital therefore warrants and justifies this study, the results of which will improve patient management.

1.3 Study objectives

1.3.1 Main Objective
To describe the effect of demographics, socio-economic background and HIV on the occurrence of posterior fossa tumors.

1.3.2 Specific Objectives

1. To describe the geographical distribution of the patients with posterior fossa tumors.
2. To describe the relationship between socio-economic status and occurrence of posterior fossa tumors
3. To describe the clinical presentation of patients with posterior fossa tumors.
4. To describe the age distribution of patients with posterior fossa tumors
5. To identify possible association of occurrence with HIV
Chapter 2

2.0 LITERATURE REVIEW

2.1 Posterior fossa anatomy

![Posterior fossa anatomy](Source-www.mayfieldclinic.com)

Fig 1 - Posterior fossa bony anatomy

The posterior fossa is between the foramen magnum and tentorium. It contains the cerebellum, medulla and pons. Anteriorly it extends to the apex of the petrous bone. Posteriorly it is enclosed by the occipital bone. Laterally, portions of the squamous and mastoid part of the temporal bone form its walls

![Contents of the posterior fossa](source-http://sccpsy101.com/home/chapter-3/section-4/)

Fig 2 - Contents of the posterior fossa
2.2 Epidemiology of posterior fossa tumors

Posterior fossa tumors are much more frequent in children than in adults. 52% of intracranial tumors occur in the posterior fossa in children. In comparison 15-20% of adult intracranial tumors occur in the posterior fossa. (3)(4). It is however apparent that literature regarding the specific parameters of epidemiology is lacking. What is especially lacking are associations of posterior fossa tumors with socio-demographic characteristics of those patients.

The most common locations are the cerebellum along with the fourth ventricle (61.5%), cerebellar hemispheres (27.5%), and brain stem (7.5%). The Male-to-female ratio is 1.35:1, and the major peak in the incidence of tumors is observed between 4 and 6 years of age. In the literature, this age range is quoted as the age group associated with most cases of posterior fossa tumors in children below 12yrs (5).

Presentation depends on anatomical site, histology and presence or absence of hydrocephalus. The pathophysiology of symptoms results from compression of vital structures or raised intracranial pressure, which include vomiting, headache, cerebellar symptoms and cranial nerve palsies (6)(7). The spectrum of presenting signs and symptoms is wide and varied but included mostly hydrocephalus, impairment of vision, incoordination and torticollis. However, there is often a combination of these signs and symptoms (8).

The commonest neoplasms of the posterior fossa are pilocytic astrocytoma, medulloblastoma, ependymoma and brainstem glioma. These have been shown to have preferences in location according to the molecular biology that was initiated during histogenesis early in fetal life. This molecular dimension has shown a correlation between the location of the tumor and prognosis in children (9). Examples include gliomas which tend to be malignant in the pons and benign in the cervicomedullary, medullopontine and tegmentum. In this study information collected included the position of the tumor on (Computed Tomography) CT scan. Literature however
demonstrates correlation between location and prognosis based on (Magnetic Resonance Imaging) MRI scans and not CT.

The developmental and anatomic approach is a reliable pre surgical identification method of the tumor and predictive of its aggressiveness(10). It is therefore possible to determine the identity, course and response to treatment from this new paradigm.

2.3 Medulloblastoma

Medulloblastoma comprise 20% of all intracranial tumors in children, making up 28.69% of posterior fossa tumors with a male predominance of 2:1. The commonest age group affected is between 3 and 12 years amounting to 49.6% in previous studies.(8)

Cytogenetic studies show that the isochromosome 17q is the most frequent abnormality in 40-50% of medulloblastomas (11) This embryonal tumor is malignant and invasive with a histopathological picture of Homer Wright rosettes in up to 40%. Classically there are densely packed cells with round to oval hyperchromatic nuclei in scanty cytoplasm (12)

(World Health Organization) WHO initially classified medulloblastomas into five groups, namely 1. classic 2. Anaplastic 3. large cell 4. Desmoplastic nodular 5. Extensive nodularity types. These were condensed into the classic, desmoplastic-nodular and large cell anaplastic. These tumors have been shown to favor particular locations in the posterior fossa. These locations are related to the histogenesis of these areas and molecular expressions unique to each site.

The classical medulloblastomas shows a preference for the 4th ventricle and usually fills it while the desmoplastic type will typically be in the peripheries of the cerebellum(13). Large cell anaplastic tumors are the most malignant and tend to show as small tumors in 4th ventricle with early dissemination. The advances in imaging have allowed an anatomical correlation between MRI and recent molecular classification of medulloblastomas.
This molecular classification is derived from specific locations expressing certain molecules that can predict both the identity of the tumor and consequent prognosis. The proposed classification is categorized as

i. (Wingless type) WNT

ii. (Sonic Hedgehog) SHH

iii. Group 3

iv. Group 4 (14).

The WNT group arises embryologically from the lower rhombic lip with strong WNT expression and is identified when centered on lateral recess of 4th ventricle. Its histology is similar to the classical medulloblastomas. WNT associated tumors are now known to have a good prognosis. SHH is expressed on the external granular layer and therefore involves the cerebellar cortex and has a good prognosis in infants but poor in older children due to presence of the (Tumor protein) TP53 mutation (15).

Group 3 and 4 occur in the vicinity of 4th ventricle. Group 3 in infants is highly malignant and is associated with (Myelocytomatosis viral oncogene) MYC amplifications and has the worst prognosis. Group 4 tumors have intermediate prognosis and do not enhance radiologically (16).

Clinical presentation commonly shows 77.7% presented with headaches and vomiting and 69.7% with papilledema and drowsiness. Nuchal pain is one of the least noted presenting features seen in 8% of patients. Disorders of vision and diplopia were noted in 17.3 and 15.9% respectively in some studies. Many will also show Cerebellar symptoms (51%) with wide based ataxia and, head tilt. Other important signs included the different forms of ataxia including truncal and appendicular ataxia. The clinical presentation is often a combination of one or more signs and symptoms.
2.4 Ependymoma

Ependymoma makes up 5-14% of all intracranial tumors. Incidence is greater in those less than 16 years with half of these ependymomas occurring in the first 36 months of life (17)(18). There is a male preponderance reported with a ratio of 2:1 (19). They are however known to occur more in the posterior fossa compared to the supratentorial and spinal ependymomas (20).

Ependymomas exist as WHO grade II and the malignant anaplastic grade III ones. The lesion in the pathogenesis of ependymomas is alteration or loss of chromosome 22 or 17. Histopathologically, ependymal rosettes are a diagnostic feature together with the presence of blepharoblasts. The picture is completed by the presence of perivascular pseudo rosettes. Microscopically, the diagnostic hallmarks are presence of microvilli, cilia, micro rosette formation and intercellular junctions. Grade II are classic ependymomas and have a low mitotic index with calcification and necrosis. Examples include clear cell, papillary and tanycytic ependymomas.

The origin of this tumor is in the radial glial cells which are in the sub ventricular zone. These are known to be different in the hemispheres (supratentorial), posterior fossa and spinal cord (21). This means ependymomas in these different locations are not the same and behave differently regarding prognosis. In the posterior fossa, age, location, histogenesis and molecular biology are used to further classify the tumors. They are then generally split into lateral (group A) and medial (group B). Group A carries a poor prognosis. Imaging in ependymomas has not been found to be very accurate hence the attempt at a molecular classification resulting in 2 basic variants namely: {Ependymoma balanced genome(anaplastic)}EPN-PFA and {Ependymoma chromosomal instability(anaplastic)}EPN-PFB(22). The first molecular variant is found in infants and has a poor prognosis while the second has a good prognosis in older children.

There have been studies attempting to show correlation between post-operative survival and micro anatomic localization. The micro anatomic categories include mid floor, lateral and roof
type. These locations affect the extent of resection. For example, the lateral type will often have involvement of nerves and vessels with prepontine extensions and renders complete resection not possible(23).

The presentation is related to the hydrocephalus, severe headache, and vomiting and gait dysfunction at a later stage. Others are ipsilateral ataxia, diplopia, irritability, retrocollis and suboccipital pain.

CT/MRI are the preferred methods of imaging. Ependymomas are midline tumors in the posterior fossa and develop mostly from the ventricular surface of the medulla. The specific locations include the obex region with cistern magna expansion, lateral recess region and prepontine cisterns. They are also known to involve the cerebello pontine angle and can extend into the upper cervical canal through invasion of the foramen of Lushka and Magendie. Leptomeningeal dissemination can rarely be demonstrated on imaging in this pathology.

Ependymomas are isodense/hyper dense with calcifications and cysts often present. With contrast media, the tumor is heterogeneously enhanced (24). On T1 weighted MRI images, they are hypo intense and on T2 sequences are hyper intense.

In the management of ependymomas, surgical resection should be the initial therapy as there is correlation between resection and prognosis. However it is not always possible to do a complete resection in 23-40% (25). Where pre-operative CSF diversion is used, its use is mainly as a temporary measure where resection is not primarily possible. However resection should be the preferred intervention on presentation.

The role of irradiation and chemotherapy for ependymomas is controversial. However 3D conformal external beam irradiation has now become the standard of care in North America for all pediatric ependymomas regardless of age in the posterior fossae after resection. When it is used, the recommended doses are from 50-55Gy in 6-8 weeks.
2.5 Astrocytoma

Astrocytomas are central nervous system neoplasms in which the predominant cell type is derived from an immortalized astrocyte. They represent 15-25% of pediatric brain tumors and 25-35% of tumors arising in posterior fossa. Peak age of presentation is 6-8 years, with no obvious sex predilection.(26).

Two main classes of astrocytic tumors are recognized. These include those with narrow zones of infiltration (e.g., pilocytic astrocytoma, subependymal giant cell astrocytoma and pleomorphic xanthoastrocytoma) and those with diffuse zones of infiltration (e.g., low-grade astrocytoma, anaplastic astrocytoma, glioblastoma). Members of the latter group share various features, including the ability to arise at any site in the (Central nervous system) CNS, with a preference for the cerebral hemispheres.

Tumor genesis of cerebellar Astrocytomas is still ill understood. However aberrations in chromosome 7 especially tandem duplication at 7q34 resulting in KIAA1549: BRAF fusion gene have been described. These aberrations cause alterations in the MEK/mitogen-activated protein kinase resulting in greater transcriptional activity and cellular proliferation.(27) This alteration does not affect outcome. Other studies have investigated correlation with prognosis in an attempt to predict outcome from molecular biology(28).

Numerous grading schemes based on histopathological characteristics have been made, including the Bailey and Cushing grading system, Kernohan grades I-IV, (WHO) grades I-IV, and St. Anne/Mayo grades 1-4.(29) Regions of a tumor demonstrating the greatest degree of anaplasia are used to determine the histologic grade of the tumor. This practice is based on the assumption that the areas of greatest anaplasia drive disease progression.
WHO grade I corresponds to pilocytic astrocytoma (80-85%), WHO grade II corresponds to low-grade (diffuse) astrocytoma (15%), WHO grade III corresponds to anaplastic astrocytoma, and WHO grade IV corresponds to glioblastoma multiforme.

Cerebellar astrocytoma grow slowly, with main symptoms of headache and vomiting in 75-95%, imbalance / gait disturbance in 25-60% and papilledema in 40-80%. Cerebellar symptoms are more likely to be seen in diffuse astrocytoma usually located in the vermis (with truncal ataxia) and cerebellar hemisphere (appendicular ataxia). In 30% of patients there is brainstem invasion and associated cranial nerve dysfunction (30)(31)(32).

MRI/CT are used to make a radiological diagnosis. T1 weighted images show hypo intense images and hyper intense on T2, with homogenous enhancement. 30% of the tumors show a classic enhancing nodule with a cyst. On CT scan, 40% show rind like enhancement with solid portion, intratumoral calcifications are detected in 10-17% of cases (33).

Total tumor resection offers the best prognosis. The patients with gross total resection have an overall five year survival rate of greater than 90%. This resection is the most important prognostic factor in progression free survival of low grade astrocytoma (34). However controversy in the treatment seems to arise from the lack of consensus on how to further manage an incompletely resected tumor or a recurrent one. Usually the decision to treat such cases is deferred until imaging proves progression or worsening of symptoms. Studies show a 5 year progression free survival of 45-65% for residual tumor of any size and long term stability of 33-65% in residual tumor (35). Spontaneous regression takes place possibly due to ischemia caused by disruption of blood supply during resection, inhibition of angiogenesis and initiation of apoptosis (36).
Radiotherapy and chemotherapy are mostly used for those tumors that recur after more than one resection. Regimens that have proved useful are carboplatin and vincristine based although they have a high rate of hypersensitivity reaction (37).

Radiotherapy in some studies does not show increase in overall survival (38), instead sometimes it’s associated with malignant transformation and side effects. Options including proton radiotherapy and stereotactic radiosurgery have shown greater safety and effectiveness in treatment for progressive and inaccessible tumors(39).

2.6 Brainstem glioma

Brainstem gliomas are an important group of tumors in the posterior fossa representing 10-20% of CNS tumors and 25% of posterior fossa tumors. The mean age at presentation is 7-9yrs with no sex predilection(32).

According to Choux et al 80% arise in the pons (40). Many other studies corroborate this and show that brainstem tumors are mostly located in the pons. In this location they are almost always malignant and present mostly in the ventral pons although some cases are ventrolateral. The pontine tumors expand craniocaudally and before invasion will cause midbrain and medullary compression.

The general forms of manifestation on imaging are diffuse, focal and exophytic. Diffuse gliomas constitute 60% of brainstem tumors in general (41). These occur more frequently in children than in adults. Onset of symptoms is usually between 6-10 years. Cranial nerve dysfunction of 5,6,7,9 and 10 are associated with diffuse glioma. It is also known that rapid progression of cranial nerve involvement predicts poor prognosis (42).
Focal brainstem gliomas can arise from anywhere on the stem with varying histology (43). They however typically arise in the midbrain and medulla and are discrete, well circumscribed without evidence of locally invasive growth. Pilocytic/fibrillary astrocytoma are the commonest gliomas in this location.

Exophytic brain stem gliomas account for 17% of brain stem tumors. They are slow growing and tend to occur in the 4th ventricle manifesting as obstructive hydrocephalus, papilledema and torticollis due to increased intracranial pressure and chronic tonsillar herniation. Low grade tumors of this type tend to grow dorsally and high grade exophytic gliomas grow laterally and ventrally.

These forms (diffuse, exophytic and focal) vary manifestation with specific locations in the brain stem. The locations include the brachium pontis, tegmentum and lateral medullary tumors. Other sites such as anterior medullary are rare but tend to be malignant when present. The tumors that occur in these regions include high grade glioma and low grade glioma.

Cervico-medullary tumors are known to be specific in behavior. They show cranial extension to as far as midpons and caudally to C6 with clear definition of boundaries in some reports. Most of the tumors here are low or high grade glioma.

Midbrain tumors are uncommon but will mostly be low grade glioma, high grade gliomas and in some cases tectal (primitive neuro ectodermal tumor) PNET. Tectal tumors may however cause difficulties in differentiation from dormant hamartomas of the peri aqua ductal region (44).
History is the mainstay of diagnoses of brainstem gliomas. Presentation depends on the location and size of the tumours. There is often cranial nerve involvement with some cases presenting with hydrocephalus for very large tumours. They may also present with quadriplegia, respiratory difficulties and motor signs as the major signs and symptoms. There is however a delay in the diagnosis because the symptoms progress slowly. Upon imaging diffuse tumors show reduced signal density on T1 weighted images and increased signal density on T2 images. Enhancement is variable and has no prognostic implications at the time of diagnoses (45).

There is presently no indication for surgery in diffuse glioma unless there is hydrocephalus and a shunt / 3rd ventriculostomy is indicated. It remains controversial how much focal brainstem glioma should be removed, debulking has only proved useful for low grade glioma although the surgical risk remains high (40).

70-80% of children experience clinical improvement when radiation therapy of 54 Gy in 30 fractions over 6 weeks was used. Survival rate is less encouraging being less than 1 year and fewer than 20% surviving for more than 2 years. Radiation in the treatment of ependymomas has been associated with induction of low grade gliomas. There is little to support the use of chemotherapy in the treatment of brainstem glioma (46).
Chapter 3

3.0 MATERIALS AND METHODS

3.1 Study design
Prospective cross-sectional study

3.2 Study setting
Parirenyatwa hospital pediatrics neurosurgical unit

3.3 Study population
All pediatric neurosurgical admissions at Parirenyatwa hospital.

3.4 Inclusion criteria
□ Patients under 12 years diagnosed by CT/MRI to have a posterior fossa tumor at Parirenyatwa hospital.

3.5 Exclusion criteria
□ Patients whose guardians did not want to participate in the study.

3.6 Sample size determination and Sampling
All patients with posterior fossa tumor diagnosis at the time of study were included. A total of 32 patients for the period from October 2013- May 2015 were enrolled.

3.7 Ethical considerations
The work was approved as an ethically sound study by Joint Research Ethics committee and the Medical Research Council of Zimbabwe.

3.8 DATA COLLECTION

After acquiring permissions from the authorities, guardians of patients under 12 years admitted at Parirenyatwa hospital and with an MRI/CT scan confirming a posterior fossa tumor were approached and taken through the consent form requesting their permission to participate in the study. Upon making sure that the form was well understood, the guardian would sign the form and grant permission to proceed with the study. All guardians were literate and were able to sign. The data collection questionnaire was administered and filled by the investigator as the guardian was being interviewed. Data was collected as per data sheet questionnaire (appendix 1).

3.9 Data analysis

Patient’s socio-demographic characteristics and measurement results for the main variables were evaluated using descriptive statistics, i.e. graphs, frequency tables etc. Proportions were used to compare differences in various categories and the standard method for comparing proportions, \( \chi^2 \) test or Fishers exact test was used. Descriptive statistics was further used to identify the most common factors associated with posterior fossa tumors in children at the referral hospital. The analysis was performed using Stata version 12.0 (Stata Corporation, College Station, Texas, USA). Means (SD) or medians (IQRs) were used where necessary.
Chapter 4

4.0 Results

A total of 32 patients presenting with posterior fossa tumors at Parirenyatwa Group of Hospitals were enrolled into the study for the period between October 2013 and May 2015. No patient was excluded from the study as per the exclusion criteria.

A total of 22(68.8%) presented with hydrocephalus and 10(31.2%) had previous ventricular peritoneal shunts inserted prior to the study period as a temporary measure while awaiting availability of theatre for resection. Figure 5 shows the study profile.

Presenting characteristics of the participants are as shown in table 1. More males 17(53.1%) compared to females presented with the condition. Mean age of the patients was 6.7(2.9) years with age ranging from 2 – 12 years. Median time to presentation from symptom onset was 3.5[2 - 6] months.

The distribution of the presenting patients by provinces was:

Manicaland 6(18.8), Mashonaland East 5(15.6), Mashonaland West 5(15.6%), Harare, 4(12.5%), Midlands, 3(9.4%), Bulawayo, 3(9.4%), Matabeleland North, 2(6.3%), Masvingo, 2(6.3%), Matebeleland south, 1(3.1%) and Mashonaland central, 1(3.1%). All patients were black Zimbabweans. A total of 7(21.7%) were HIV positive.
Fig 3: Origin of patients by province

Fig 4 – Provincial population figures
Figure 5: Study profile
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean(SD)</td>
<td>6.7(2.9)</td>
</tr>
<tr>
<td>Age group distribution</td>
<td></td>
</tr>
<tr>
<td>0 – 3</td>
<td>3(9.4)</td>
</tr>
<tr>
<td>4 – 6</td>
<td>15(46.9)</td>
</tr>
<tr>
<td>7 – 10</td>
<td>10(31.2)</td>
</tr>
<tr>
<td>11 – 12</td>
<td>4(12.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17(53.1)</td>
</tr>
<tr>
<td>Female</td>
<td>15(46.9)</td>
</tr>
<tr>
<td>Province of origin</td>
<td></td>
</tr>
<tr>
<td>Matebeleland North</td>
<td>2(6.3)</td>
</tr>
<tr>
<td>Manicaland</td>
<td>6(18.8)</td>
</tr>
<tr>
<td>Mashonaland West</td>
<td>5(15.6)</td>
</tr>
<tr>
<td>Midlands</td>
<td>3(9.4)</td>
</tr>
<tr>
<td>Masvingo</td>
<td>2(6.3)</td>
</tr>
<tr>
<td>Harare</td>
<td>4(12.5)</td>
</tr>
<tr>
<td>Bulawayo</td>
<td>3(9.4)</td>
</tr>
<tr>
<td>Mashonaland East</td>
<td>5(15.6)</td>
</tr>
<tr>
<td>Mashonaland central</td>
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<tr>
<td>Matebeleland south</td>
<td>1(3.1)</td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7(21.9)</td>
</tr>
<tr>
<td>Negative</td>
<td>25(78.1)</td>
</tr>
<tr>
<td>Time (months) to presentation from symptom onset, median [IQR]</td>
<td>3.5[2- 6]</td>
</tr>
</tbody>
</table>

**Table 1- Characteristics of the study patients**
The 4 – 6 year age group had the highest frequency of the condition at 47%.

Characteristics of the mothers
The median age of the mothers was 31[27-35] IQR years mostly with Christian background. Information about 4 mothers who did not present for various reasons with the patient was provided by the relative accompanying the child (Table 2). Their HIV statuses were not known. From the 28 mothers who presented with the patients, 3(9.4%) were known to be HIV positive. The majority of the mothers had completed “O” Level education and were married as shown in table 2. A total of 23(71.9%) of the mothers had parity ≥3. The median age of the mothers at delivery was 24[21 30] IQR years.

Figure 6: A pie chart of the distribution of disease by age group
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), Median [IQR]</strong></td>
<td>31[27 35]</td>
</tr>
<tr>
<td><strong>Age (years) at delivery, Median [IQR]</strong></td>
<td>24[21 30]</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5(15.6)</td>
</tr>
<tr>
<td>2</td>
<td>4(12.5)</td>
</tr>
<tr>
<td>3</td>
<td>11(34.4)</td>
</tr>
<tr>
<td>4</td>
<td>7(21.9)</td>
</tr>
<tr>
<td>≥5</td>
<td>5(15.6)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3(9.4)</td>
</tr>
<tr>
<td>Married</td>
<td>22(68.8)</td>
</tr>
<tr>
<td>Separated</td>
<td>6(18.8)</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>11(34.4)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1(3.1)</td>
</tr>
<tr>
<td>Trader</td>
<td>5(15.6)</td>
</tr>
<tr>
<td>Professional</td>
<td>4(12.5)</td>
</tr>
<tr>
<td>Subsistence farmer</td>
<td>11(34.4)</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>8(25.0)</td>
</tr>
<tr>
<td>‘O’ Level</td>
<td>21(65.6)</td>
</tr>
<tr>
<td>‘A’ Level</td>
<td>2(6.3)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>1(3.1)</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4(12.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>3(9.4)</td>
</tr>
<tr>
<td>Negative</td>
<td>25(78.1)</td>
</tr>
<tr>
<td><strong>Religion</strong></td>
<td></td>
</tr>
<tr>
<td>Christianity</td>
<td>30(93.7)</td>
</tr>
<tr>
<td>Other</td>
<td>2(6.3)</td>
</tr>
</tbody>
</table>

**Table 2- Characteristics of the mothers**
Clinical presentations of patients

Patients presented with a clinical manifestation of hydrocephalus in 22(68.8%). This was usually in combination with other associated signs and symptoms. The other 10(31.3%) had prior VP shunts and presented primarily for elective resection. The most prevalent presenting symptoms among the patients included headache in 28(87.5%) of the patients, ataxia in 27(84.4%) and head tilt in 18(56.3%) of patients. The rest of other presenting symptoms associated with posterior fossa tumor are shown in figure 5.

![Clinical presentation of patients](image)

**Figure 7- Clinical presentation of patients**
Figure 8 — Patient outcomes

All patients with posterior fossa tumors in study
N=32

Patients diagnosed with posterior fossa tumor and hydrocephalus in whom only a VP shunt was inserted
N=22
Outcome
Deceased N=4
Discharged N=18

Patients with VP shunts already inserted coming for resection of tumor
N=1
Outcome
Discharged N=18

Patients with VP shunts and resected
N=9
Outcome
Deceased N=2
Discharged N=7
**Figure 9 – Tumor location in the study patients**

**Histology of resected tumors**

1. Astrocytoma n= 4
2. Ependymoma n=2
3. Medulloblastoma n=2
4. Choroid plexus papilloma n=1

**Fig 10- Pie chart showing the histology of resected tumors**

The 4 patients with astrocytoma had respectively low grade, high grade and 2 pilocytic types.
Chapter 5

5.0 Discussion

The sociodemographic characteristics show that the commonest posterior fossa tumor occurrence was in the age range 4-6yrs as shown in other literature(5). The youngest patient was 2yrs old while the oldest was just below 12yrs. There was a male preponderance of 1.13:1 compared to females, literature shows a ratio of 1.35:1. The mean age of presentation was 6.7 years and was similar to known literature(7). The oldest and the youngest among the study patients had fewer posterior fossa tumors compared to the 4-6yr group.

In our setting, ventriculoperitoneal shunts were inserted as a temporary measure for hydrocephalus while awaiting resection. In these patients, no upward herniation was observed. Reasons for not resecting tumor as first choice in the 22 patients who had ventriculoperitoneal shunts inserted on initial admission are:

1. Number of operating days allocated to neurosurgery is only 2 per week for both adults and pediatric patients with each list running from 0800 to 1300hrs. As a consequence, there were at least 250 patients on the neurosurgery waiting list for various other conditions. There is therefore a profound lack of theatre time as we share theatres with other specialties on different days.

2. Intensive care unit has only 7 beds for our 1000 bed hospital. These are allocated preferentially to patients admitted as emergencies and the remaining ones are made available for elective surgeries. It therefore means that the availability of the beds is unpredictable and often has to be confirmed on the day of the surgery resulting in numerous cancellations on the day of the procedure. With each posterior fossa surgery requiring post-operative intensive care, it was not possible most of the time to secure an ICU bed hence fewer resections were done.
3. Shortage of operating materials including essential chemical hemostats such as surgicel and some instruments such as a working bipolar pencil. Most of the time patients could not afford to source these materials hence the failure to operate.

4. Some patients did not turn up for booked elective resections opting for traditional/spiritual alternative treatment. Reasons included fear of the operation, frustration due to long waiting periods and lack of finance for another trip to the central hospital.

These reasons resulted in only 28.1% of patients being operated from 2013-2015, an appalling figure which must be urgently addressed. In raw figures, the operation rate was an average of 3 per year against 10 patients presenting in our unit in the same year, this is clinically and ethically unsound and a case for removal of obstacles must be made. Further to this was a mortality of 18.1% in those that were not operated. This figure is high and as long as disease progression is not halted, patients with posterior fossa tumors will continue to succumb. As long as the operation rate is low, it remains difficult to convince those who sought alternative treatment elsewhere to come for resection as there are no guarantees they will be assisted. Much can be done in our study setting to ensure that these children are operated on in time by providing the necessary resources.

A literature search did not reveal any particular geographical preponderance anywhere. In our study, the catchment of the study population was representative of the geographical areas of the country with more inhabitants from the northern part of the country compared to the south. Our patients came from all the 10 provinces of the country. It was shown that the northern parts generally had more cases than the south. It is also worth noting that the top 4 Northern provinces by presentation were intimately related and bordered each other. These were namely
Manicaland, Mashonaland (east, west) and Harare. It is possible there may be a geographical factor/s which cannot be concluded in this study. It may also be assumed for now that this picture is due to the north having more inhabitants than the south.

Possible reasons for this include more health facilities in the north compared to the rest of the country. Another possible reason is that there is increased awareness of the condition in those areas compared to the others. There is however no publication to support this for our study patients. No literature currently supports a possible physical etiological agent which may be unique to a geographical location.

Researchers have however implicated cured meats and exposure to polycyclic aromatic hydrocarbons through smoking or occupational sources. Other reports cite pesticides, petrochemical products and exhaust fumes but this remains unproven. Discussions on the association of these agents with posterior fossa tumors is highly controversial. Potentially it may be reasonable to study patients whose mothers were exposed in factories, farms etc., where exposure to the above mentioned agents is higher than the general population. Such possibilities warrant more research in posterior fossa epidemiology.

The question about whether there is a link between the socio economic status and the occurrences of posterior fossa tumors remains unanswered in literature. Maternal characteristics studied included average age at delivery, median age, parity, marital status, occupation, highest education level achieved, HIV status and religion. We attempted to demonstrate how the social circumstances of our patients collated with occurrence of posterior fossa tumors in the under 12 years group. In our study, the majority of the patients were poor with unemployed mothers and a family income of under $500 per month with no basic medical insurance. It was also important to note that most of the patients came from rural areas. The mothers with affected
children were mostly of a parity greater than 3 with average age at delivery at 24 years. The average age of the mothers at presentation was 31 years. Most of the women (68.8%) were subsistence farmers and housewives of very little income. Generally all the women were literate with the majority having reached ‘O’ level.

The correct inference from this aspect of data is not on the occurrence of the tumors per se. A demonstration of adverse social circumstances may reveal a major factor in causing delayed presentation of patients noted to be 3-5 months. Lack of financial resources may have contributed to the delay in getting treatment as patients failed to visit even their local hospitals in time for an early referral to our center. Seeing the large number of patients that had to seek alternative means of treatment, it is clear that lack of financial resources played a part in reducing the number of patients returning for operations. Tied with this were the spiritual beliefs of the guardians who sought spiritual respite from prophets and traditional healers. In our data, it was shown that all patients had specific religious inclinations. It is also possible that some of these patients may have been forced to seek alternate treatment because of the long waiting time for the surgery. It is known in literature that earlier intervention is associated with good outcomes and that diminished resources or poverty of the patient indirectly leads to their poor outcome(49).

Our patients were both of limited financial means and did not get the definitive intervention at the time of presentation. Their outcome was therefore poor with a mortality of 18.2% in the unresected patients during admission.

The presentation of our patients was similar to the presentation described in literature. Prominent signs included headache, ataxia and hydrocephalus. They were mostly pressure symptoms
resulting from enlargement of the tumors and compression of the cerebellum and causing subsequent obstructive hydrocephalus(50).

One of the first signs to be noticed by most caregivers was ataxia observed as abnormal walking by guardians. Unfortunately, guardians would seek attention at a later period hoping that the ‘abnormal walking’ would abate spontaneously. By the time of presentation at Parirenyatwa hospital, there was manifestation of other signs. Different guardians gave similar accounts of their affected children walking ‘as if drunk’ or swaying when walking.

Posterior fossa tumors can affect children from below 1yr but in our study, the youngest patient was 2years and the oldest was just under 12years. A possible explanation could be the difficulty in noticing early signs such as ataxia in ages below 2years that are just starting to walk by usual milestones of between 14-18months. It is therefore difficult to pick up such signs until symptoms of raised intracranial pressure from secondary hydrocephalus appear. From our data, projectile vomiting was an important reason for presentation. Consequently by this time, the tumor would have grown large enough to cause obstructive hydrocephalus and in some cases reduce chances of gross total resection.

In this study every patient was offered HIV testing. The tests offered included antibody testing. This was in line with the current Zimbabwean health ministry policy allowing for and encouraging provider initiated testing.

Data show that the estimated prevalence of HIV in the 0-14yr age group ranged from 3.64 % (2011) - 2.37 %(51). 21.9% of our patients up to 12yrs of age were HIV positive, a remarkably higher crude rate than the national average. This translates to a rate 600% more than the population. The tremendous difference between the population HIV rate and our patients cannot be
ignored. It raises questions about a possible link in patients exposed to HIV from birth. If indeed there is a link, then HIV control and prevention may have an effect on the occurrence and progression of posterior fossa tumors. It was not possible to compare HIV rates in our patients with those from the rest of the pediatric unit including the oncology department as there were no specific documented rates of admitted patients. It may be worthwhile to study the relationship of HIV and other oncological conditions in pediatric patients.

There is however no data in literature to back this probable association. The available data has loosely implicated ‘viral’ infections with no evidence of accepted levels. The exposure to viral infections by the mother during gestation has been hypothesized to increase the odds of childhood tumors including those of the posterior fossa. Identification of these viruses will theoretically help interventions in prevention of childhood brain tumors. It is therefore worthwhile to pursue a larger study to prove association with HIV of statistical significance.

The Majority (78.1%) of our study patients were HIV negative. With HIV being one of the commonest conditions in our setting, it was important to determine possible correlation but there was none to be inferred.

The in-hospital mortality in the entire study period was 18.8%. Mortality occurred in 2 patients who had tumor resection and 4 died in those who did not have a resection despite having ventriculoperitoneal shunts. The patients who died after tumor resection included an on table death during surgery after unresponsive bradycardia followed by cardiac arrest while the second died in the first 24hrs of resection post operation. The post mortem in this patient revealed conning as the cause of death. Of the remaining patients who had no resection, 4 patients died as a result of disease progression. However, the impairment of function was better in those with surgical
intervention either as ventriculoperitoneal shunt or resection at discharge. It is thus our recommendation that tumor resection be aimed for in the shortest possible time and where resources do not permit, it is worthwhile placing a ventriculoperitoneal shunt early (52).

The discharged patients were semi ambulant to ambulant with scores from 1 to 5 based on the functional ambulance category. At least 70% of the surviving patients had scores from 4 to 5, the rest were semi ambulant with scores from 1-3. These described patients ranged from those that where dependent to those that functioned independently(53). Although there was reduction in pressure symptoms such as headaches and hydrocephalus after both resection and ventriculoperitoneal shunt insertion only, in our study there was persistence of ataxia and impaired vision. These signs were observed to be irreversible regardless of the procedure(54).

5.1 Conclusion

1. Posterior fossa tumors at Parirenyatwa are referred mostly from Manicaland.

2. The commonest age of presentation is 4-6yrs.

3. Posterior fossa tumors at Parirenyatwa hospital are more common in males

4. Clinical presentation is mostly as a result of complications due to raised intracranial pressure

5. There was an in-hospital mortality of 18.8%

6. Given the higher proportion of our study patients with HIV compared to the pediatric population, they may be an association with HIV which may warrant a study with a bigger sample size.
6. Limitations of the study

1. Small number of patients with the posterior fossa tumors studied over a limited time frame hence reduced sample size and follow-up.
2. All diagnoses were based on radiological appearances of the tumors, it is possible that some of the unconfirmed cases may be other pathology.
3. Inadequately allocated theatre time hence few confirmed histologies.
4. Although Parirenyatwa hospital is the only public neurosurgical unit in the country, there are at least 3 private hospitals offering neurosurgery. Our findings are therefore not be representative of all the posterior fossa tumors in Zimbabwe.

7. Recommendations

1. Increase awareness of posterior fossa tumors especially in the populations at risk and the healthcare personnel in provinces.
2. Increase number of health facilities in the southern part of Zimbabwe.
3. Increase availability of imaging such as CT/MRI at provincial and district hospitals.
4. Provide dedicated pediatrics theatre time with guaranteed post-operative intensive care facilities. The system should ensure that the care of posterior fossae tumour patients is according to international standards which recommend urgent resection in the shortest possible time.
5. A longer duration study is necessary, this current one may serve as a pilot study for the future expansion of the study.
8. References


10. Gilbertson RJ, Gutmann DH. Tumorigenesis in the brain: Location, location, location.


27. Ida CM, Lambert SR, Rodriguez FJ, Voss JS, Mc Cann BE, Seys AR, et al. BRAF Alterations Are Frequent in Cerebellar Low-Grade Astrocytomas With Diffuse Growth


Appendices

Appendix 1

QUESTIONNAIRE

1. Patient Information
   - Patient ID……….
   - Hospital number: …………………
   - Province………………………….
   - District ………………………….
   - Date of birth: ………./………./……….
   - Age (in years): …………M…F…….
   - Race:
     1. Black
     2. White
     3. Other (specify) …………………………….
   - HIV Status
     1. Positive
     2. Negative
     3. Unknown
   - Time since onset of initial symptoms to presentation …………………months
   - Date of start of clinical management …………/………/……….
   - Date of initial treatment ………/………/……….

2. Maternal Information
   - Date of birth ………./……….
   - Age (in years) ………………….
c) Age at delivery (years) ............

d) Parity:
   1. Para 1
   2. Para 2
   3. Para 3
   4. Para 4 and above

e) Marital Status
   1. Single/never married/not cohabiting
   2. Single/never married/cohabiting
   3. Married/monogamous
   4. Married/polygamous
   5. Widowed/divorced/separated

f) Occupation
   1. Housewife
   2. Unemployed
   3. Trader/hawker/semi-skilled
   4. Professional
   5. Subsistence farmer

g) Monthly income
   1. < $500
   2. $500 – $1200
   3. >$1200

h) Level of education
1. Primary
2. ‘O’Level
3. ‘A’ Level
4. Tertiary

i) Residence (stay > 6 months in a year)
   1. Urban
   2. Rural
   3. Farm
   4. Resettlement area/peri-urban

j) Health insurance/Medical Aid
   1. No medical aid
   2. Basic cover medical aid

k) HIV status
   1. Unknown
   2. Positive
   3. Negative

l) Religion
   1. Christianity
   2. Other

3. Clinical presentations of patients
1. Hydrocephalus
2. Headache
3. Drowsiness
4. Diminution of vision
5. Vomiting
6. Dizziness
7. Speech disturbance
8. Incoordination
9. Multiple cranial nerve palsy
10. Neck pain
11. Ataxia
12. Head tilt

5. Diagnostic Imaging used

1. Date ……/…… /……
2. CT scan ………………………
3. MRI ………………………..

6. Location of tumors

1. Fourth ventricle
2. Cerebella hemisphere Left/Right
3. Brain stem
4. Cerebellar vermis
7. Procedure offered as treatment
   1. Pre-resection V-P Shunt
   2. Resection Complete
   3. Resection incomplete

8. Histological diagnosis ...................................................

9. N........... Y..........

10. Posterior fossa tumor type ....................................................

11. Outcome
   1. Discharge date ........../....../.........
   2. Mortality Date of death....../....../.........

12. Deficits at discharge
   □ Ambulatory
   □ Cranial nerves
   □ Ataxia
   □ Dysarthria

12. Notes
   ...............................................................................................
Appendix 2

Consent form

English

I……………………………….guardian to…………………………..agree to participate in the posterior fossa study having been duly informed of the conduct of the study, in the full knowledge that participation will not disadvantage the patient in my custody.

Signature……………………………..Witness………………………………

Appendix 3

Shona

Ini……………………………………somuchengeti pamutemo wa……………………………………………………ndinobvuma kunge ndichibatanidzwa mutsvakiso dzegomarara re mumusoro ndaziviswa zvizere kuti mwana haazokoneswe kurapwa netsvakiso iyi.

Signature……………………………..Witness………………………………
Appendix 4

Ndebele

Mina..........................................................Ogcina u............................................Ngiyavuma ukuba yingxeny e yesifundo emva kokuchasiselwa ukuthi kungeke kube yingozi enganeni yami

Signature........................................Witness........................................