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DEPARTMENT OF ANATOMY

ASSESSMENT OF THE PREVALENCE AND ASSOCIATED RISK FACTORS WITH PEDIATRIC HYDROCEPHALUS IN SELECTED DIAGNOSTIC CENTERS IN ADDIS ABABA, ETHIOPIA

THESIS SUBMITTED TO ANATOMY DEPARTMENT, SCHOOL OF MEDICINE ADDIS ABABA UNIVERSITY FOR PARTIAL FULFILLMENT OF THE REQUIREMENT OF MASTERS IN ANATOMY

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DECLARATION

I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate. I have followed all the ethical principles of scholars in the preparation of the proposal, data collection, data analysis, and completion of this thesis. All scholarly matter that is included in this thesis has been given recognition through citation. I affirm that I have cited and referenced all sources used in this thesis. Every effort has been made to avoid plagiarism in the preparation of this thesis. This thesis is submitted in partial fulfillment of the requirement of the Master's degree in Anatomy from Addis Ababa University, College of Health Sciences; School of Medicine. This thesis will be deposited in the Library of Addis Ababa University and will be available to local, national, and international scientific communities.

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TABLE OF CONTENTS

IDENTIFICATIONS i
DECLARATION ii
ACKNOWLEDGMENTS iii
ACRONYMS AND ABBREVIATIONS vii
LIST OF TABLES viii
LIST OF FIGURES ix
ABSTRACT x
1. INTRODUCTION 1
1.1. Background 1
1.2. Statement of the Problem 1
1.3. Significance of the Study 3
2. LITERATURE REVIEW 4
2.1. What is Hydrocephalus (HCP) 4
2.2. Epidemiology of HCP 4
2.3. Types of HCP 5
2.4. Risk Factors Associated with Pediatric HCP 5
2.5. Diagnosis of HCP 6
2.6. Treatments, treatment failures and complications of HCP 9
2.7. Management of HCP 9
2.8. Conceptual/Theoretical framework 10
3. RESEARCH OBJECTIVES 12
3.1. General Objectives 12
3.2. Specific Objectives 12
4. METHODOLOGY 13
4.1. Study Setting and Period 13
4.2. Study Design 13
4.3. Source Population 13
4.4. Study Population 13
4.5. Sample Size and Sampling Technique 14
4.6. Inclusion and Exclusion criteria 14

4.6.1. Inclusion Criteria 14
4.6.2. Exclusion Criteria 14
4.7. Variables 15
4.7.1. Independent Variable 15
4.7.2. Dependent Variables 15
4.8. Operational Definition 15
4.9. Data Collection Instrument 16
4.10. Data Collection Procedure 16
4.11. Data Quality Control 16
4.12. Data Analysis 17
4.13. Ethical Consideration 17
4.14. Dissemination and Utilization of Results 17
5. RESULTS 18
5.1. Characteristics of Study Participants of the Retrospective Study 19
5.2. Characteristics of Study Participants of the Prospective Study 19
5.3. Prevalence and Types of Pediatric HCP from Retrospective Study 22
5.4. Prevalence and Types of Pediatric HCP from the Prospective Study 23
5.5. Risk Factors Associated with HCP in the Retrospective Study 24
5.6. Risk Factors Associated with HCP in the Prospective Study 24
5.7. Prevalence of Congenital and Acquired Hydrocephalus 27
5.7.1. Prevalence of Congenital and Acquired HCP within the Retrospective Study 27
5.7.2. Prevalence of Congenital and Acquired HCP within the Prospective Study 29
6. DISCUSSIONS 33
6.1. Demographics: Sex, Age and Patient Characteristics of both studies 33
6.2. Prevalence of HCP 34
6.3. Prevalence of Congenital and Acquired HCP 35
6.3.1. Aqueductal stenosis and Neural tube defects (NTDs) 35
6.3.2. Post-infectious HCP (PIH) 36
6.3.3. HCP secondary to Tumors and Adhesion of Foramen of Monroe 37
6.3.4. Post-Hemorrhagic HCP 38
6.4. Imaging investigations 39

6.4.1. Computed tomography (CT) 39
6.4.2. Magnetic resonance imaging (MRI) 40
6.5. The Risk Factors Associated with Pediatric HCP 40
6.5.1. Prenatal care given to mothers and HCP 40
6.5.2. Folic acid Supplementation and HCP 41
6.5.3. Advanced maternal age and HCP 42
6.5.4. Familial Association and HCP 43
6.5.5. Sex preference of HCP 44
6.5.6. Maternal parity and multiple pregnancy and HCP 44
6.5.7. Trauma during Pregnancy 44
6.5.8. The Educational Level of the Mother 45
6.5.9. Maternal Pathologies, Infections, Smoking, Illicit drug use, and Maternal Medication 46
7. STRENGTH OF THE STUDY 48
8. LIMITATIONS OF THE STUDY 49
9. CONCLUSIONS 50
10. RECOMMENDATIONS 52
11. REFERENCES 53
12. ANNEXES 57
Annex 1- Consent Form (English Version) 57
Annex 2- Questionnaire 59

ACRONYMS AND ABBREVIATIONS

HCP- Hydrocephalus

MRI- Magnetic Resonance Imaging

CT- Computed Tomography

CSF- Cerebrospinal fluid

ICP- Intra-cranial pressure

IVH-Interventricular hemorrhage

CNS- Central Nervous System

NTDs-Neural tube defects

VP shunt-Ventriculoperitoneal shunt

MMC- Mennigomyocele

NPH- Normal-pressure hydrocephalus

PIH-Post-infectious hydrocephalus

NPIHC-Non post-infectious hydrocephalus

LIST OF TABLES

Table 1. Characteristics of Study Participants of the Retrospective Study within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020……19

Table 2. Characteristics of Study Participants of the Prospective Study within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020……21

Table 3.Associated Risk factors of Hydrocephalus (HCP) of the Retrospective Data within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020……24

Table 4. Associated Risk factors of HCP of the Prospective data within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020……26

Table 5. Congenital Etiologies of Pediatric HCP- Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-20……28

Table 6. Acquired Etiologies of Pediatric HCP- Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020……28

Table 7. Tumor Related Etiologies of Pediatric HCP- Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020……28

Table 8. Post-hemorrhagic HCP Etiologies Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020……29

Table 9. Congenital and Acquired Etiologies of Pediatric HCP- Prospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-.2020……30

Table 10. Tumor Related Etiologies of Pediatric HCP- Prospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020……30

Table 11. Post-hemorrhagic HCP Etiologies Prospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020……30

LIST OF FIGURES

Figure 1. Heavily T2W 3D-SPACE images of different cases……..7

Figure 2. Non-Communicating Hydrocephalus……..8

Figure 3. Pediatric Hydrocephalus cases confirmed by Radiologist within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020……22

Figure 4.Type of Hydrocephalus confirmed by Radiologist within the selected diagnostic centers in Addis Ababa, Ethiopia, 2018-2020……22

Figure 5.Hydrocephalus confirmed by Radiologist within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020……23

Figure 6. Type of Hydrocephalus confirmed by Radiologist within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020……23

Figure 7- MRI image represented by T2 Sagittal, T1 Axial and T2 Coronal FLAIR Dark fluid……31

Figure 8- MRI image represented by T2 Axial, T2 Sagittal, and T1 Coronal- Post-contrast enhanced sequences……31

Figure 9- MRI image represented by T2 Sagittal and T2 Axial sequences……32

Figure 10. MRI image represented by T2 Axial, T1 Axial sequences……32

ABSTRACT

Background: Hydrocephalus (HCP) is defined as pathophysiology with disturbed CSF. Neither qualitatively nor quantitatively are there adequate data to determine the prevalence and incidence of HCP in the developing world. HCP is a treatable condition that when left untreated, has fatal consequences.

Objective: The objective of this study, therefore, was to assess the prevalence and associated risk factors in pediatric HCP in selected diagnostic centers in Addis Ababa, Ethiopia.

Methods: A cross-sectional facility-based study was conducted over a retrospective and prospective data collection periods. Children aged 5 years and below who came to the four selected diagnostic centers for MRI and CT examination were studied. The collected data were analyzed using binary logistic regression. The level of significance was set at $P<0.05$.

Result: The retrospective study included 639(58%) males, 432 (42%) females, and 753 (68.4%) infants were aged younger than 24 months. The mean age calculated was 22.3 months. Children diagnosed with HCP were 245 (22.3%); of these HCP cases, 153(62.4%) were classified as non-communicating HCP. Aqueductal stenosis, 17.9% was found to be the most common cause associated with congenital HCP. This study identified infants aged younger than 24 months to be significantly associated with HCP ($P<0.05$). Regarding the gender and age distribution of the prospective study, 57(57.6%) males, 42 (42.4%) females, mean age of 24.9 months, and 60 (60.6%) infants aged younger than 24 months were included. Children diagnosed with HCP were 23 (23.2%); of these HCP cases, 13(56.5%) were classified as non-communicating HCP. This study also found Aqueductal stenosis 26.1% as the most common cause associated with congenital HCP. Inadequate consumption of folic acid, usage of the folic acid supplement after conceiving, and familial association of HCP were all found to be statistically significant ($P<0.05$).

Conclusion: The results of this study suggest that the high prevalence of HCP was due to the high prevalence of Aqueductal stenosis and NTD; with a small contribution of post-infectious causes. The majority of infants who present with HCP are aged younger than 24months.

Key Words: Hydrocephalus, Cerebrospinal fluid, Neural tube defects, CT, and MRI.

1. INTRODUCTION

1.1. Background

Hydrocephalus (HCP) is defined as a pathophysiology with disturbed cerebrospinal fluid (CSF) circulation (1). HCP is a common disorder of CSF physiology resulting in abnormal expansion of the cerebral ventricles. Infants commonly present with progressive macrocephaly whereas children older than 2 years generally present with signs and symptoms of intracranial hypertension (2).

Infant HCP can be congenital or acquired (3). In the developed world, the incidence of congenital HCP has been estimated to be about 0.5 cases per 1000 live births and the overall incidence of neonatal HCP is estimated to be about 3 to 5 cases per 1000 live births (4).
The annual incidence of infant HCP in sub-Saharan Africa is unknown. However, from available literature, the burden of infant HCP in East Africa is significant, with more than 6,000 new cases estimated per year. The majority is caused by neonatal infection, and should thus be preventable. With about 1 neurosurgeon per 10,000,000 people in East Africa, initial treatment for HCP is often unavailable (3).

In Ethiopia, the etiology and incidence rates of HCP can be assumed to correspond to what has been reported from other East African countries, where HCP has been estimated to have an infectious origin in the majority of cases because of a much higher prevalence of untreated neonatal or even prenatal infections (5). For example in Uganda, post-infectious HCP (PIH) is calculated to account for as much as 60% of the total pediatric HCP patient population. Several factors probably contribute to this high incidence of central nervous system (CNS) infections, including malnutrition and consequently a lowered resistance to infections (6).

According to extrapolated estimates, there will be approximately 6,000 new cases per year in East Africa and 45,000 new cases of pediatric HCP in Sub-Saharan Africa (6). If these estimates from Uganda are valid also for Ethiopia, one can expect between 2,000 and 4,000 new cases of pediatric HCP per year (5).

There are several types of HCP, which are characterized based on the location of the CSF accumulation, (7) communicating HCP, in which flow is not obstructed, but CSF is inadequately reabsorbed in the subarachnoid space and the non-communicating HCP or the obstructive type, in which flow of CSF from the ventricles to subarachnoid space is obstructed (8). Medical therapy involves decreasing the production of CSF. The most common surgical treatment is the placement of a ventriculoperitoneal shunt. Postoperative complications may include infection, blockage, drainage abnormalities, and mechanical failure (7).

Several key risk factors have been identified to be strongly associated with the development of congenital HCP in an infant. The prevalence of familial patterns of inheritance for congenital HCP suggests a broader role for genetic factors in the pathogenesis of congenital HCP (9).

1.2. Statement of the Problem

In developed countries, the incidence of congenital HCP is estimated at three to five cases per 1000 live births (4). The causes of congenital HCP can be divided into primary (idiopathic) or secondary (acquired) causes, with the majority being idiopathic in origin. Excluding secondary HCP and that associated with Spinal Bifida, the incidence of primary congenital HCP has been estimated at 0.2 to 0.8 per 1000 births (4).

Neither qualitatively nor quantitatively are there any adequate data/literature to determine the prevalence and incidence of HCP in the developing world, especially in sub-Saharan Africa, where this condition appears to be much more frequent than in developed countries. Taking some very conservative estimates in Uganda, as an example, between 1000 and 2000 new cases of infant HCP occurs every year, with this most likely being an underestimate. Extrapolating this to other regions suggests 6500 new cases per year in East Africa and more than 45,000 new cases per year in sub-Saharan Africa. The timely treatment of these infants presents an enormous challenge given not only the economic and infrastructural constraints on families and facilities but also the relative paucity of neurosurgeons in the region, with an overall ratio of about 1 neurosurgeon to 10 million people in East Africa (Uganda, Tanzania, and Kenya) (3).

HCP is a common neurosurgical disorder that can lead to significant disability or death if not promptly identified and treated. Data on the burden of HCP in low-income countries are limited, given a lack of radiologic resources for the diagnosis of this condition (10).

HCP has many causes. Congenital HCP, most commonly involving aqueduct stenosis, has been linked to genes that regulate brain growth and development. HCP can also be acquired, mostly from pathological processes that affect ventricular outflow, subarachnoid space function, or cerebral venous compliance (2).

In Ethiopia, the etiology and incidence rates of HCP can be assumed to correspond to what has been reported from other East African countries, where HCP has been estimated to have an infectious origin in the majority of cases because of a much higher prevalence of untreated neonatal or even prenatal infections. Only a minute fraction of children with HCP in Ethiopia – a few

hundred each year - are diagnosed and receive proper treatment for their HCP. This probably means a selection bias that makes it difficult or even impossible to determine or estimate the general characteristics of HCP in Ethiopia concerning etiology, type of HCP, gender, or age composition of the patients. If the estimates on new cases of pediatric HCP in Ethiopia are valid, these children represent an enormous challenge for the nation, not only for diagnostic but also for surgical capacity (5).

Routine measurements of the head circumference (HC, also termed occipitofrontal circumference) have proved effective in the early detection of HCP; such routine measurements identify children with HCP more commonly than clinical symptoms (11).

Ventriculoperitoneal (VP) shunt insertion has been the mainstay of treatment, but over the last years, endoscopic third ventriculostomy (ETV) with or without choroid plexus cauterization has come into the picture. VP shunt insertion is associated with high complication and failure rates. Worldwide, complication rates range widely, from 1% - 40%; shunt infections probably being the most frequent cause of failure. Studies from so-called developed countries have over the years reported an incidence of shunt infection varying from 0 - 27 % per procedure (12, 13). Shunt and endoscopic treatment approaches should be individualized to the child. The long-term outcome for children that have received treatment for HCP varies. Advances in brain imaging, technology, and understanding of the pathophysiology should ultimately lead to improved treatment of the disorder (2).

This study has assessed and presented an analysis of the prevalence and associated risk factors of pediatric HCP from a large sample of CT and MRI scans of the head performed at the selected diagnostic centers in Addis Ababa, Ethiopia, a low-income country in Africa.

1.3. Significance of the Study

- The results of this study will help in the identification of the prevalence and the risk factors that are associated with pediatric HCP.

- The findings of this study will contribute to the understanding of the pathophysiology and give focus on the management of HCP.

- Furthermore, this study will help Radiologists and Radiologic Technologists understand the predominance of this condition for better diagnosis of their patients. Also, it will build a better understanding of the advantages of neuro-radiography for other health professionals for better outcome of patients.

- Moreover, this study will create awareness for the importance of prenatal care given to mothers during their pregnancy.

2. LITERATURE REVIEW

2.1. What is Hydrocephalus (HCP)

HCP is a common disorder of CSF physiology resulting in abnormal expansion of the cerebral ventricles. CSF secreted by the choroid plexus epithelium in the cerebral ventricles flows into the subarachnoid spaces and enters the cerebral venous system via the arachnoid granulations. (2) CSF surrounds the brain and spinal cord, acting as a protective cushion against injury. It carries nutrients and proteins to the brain while carrying waste products away from surrounding brain tissue. Under normal conditions, there is a balance between the amount of CSF that is produced and the rate at which it is absorbed. HCP is caused most often by an obstruction to the flow pattern of the CSF, but may also result from a failure of CSF to be absorbed into the bloodstream. Because CSF is produced continuously, when interference with absorption or flow of spinal fluid occurs, CSF will begin to accumulate, causing the ventricles to enlarge and pressure to increase inside the head. When the blockage occurs within the ventricular system, it is called **non-communicating HCP.** If the blockage occurs in the subarachnoid space (outside the ventricles), it is called **communicating HCP**, meaning that the ventricles remain open and communicate with each other and the subarachnoid spaces, but CSF cannot be fully absorbed into the bloodstream (14).

2.2. Epidemiology of HCP

Infant HCP can be congenital or acquired. In the developed world, the incidence of congenital HCP has been estimated to be about 0.5 cases per 1000 live births and the overall incidence of neonatal HCP is estimated to be about 3 to 5 cases per 1000 live births (3). The observed prevalence of congenital HCP reported in the northern region of China, from 357 congenital HCP cases, had a rate of 20.3 HCP cases per 10,000 births. Of the congenital HCP cases, 146 were isolated congenital HCP cases, accounting for 41% of the total congenital HCP cases and resulting in a prevalence rate of 8.3 per 10,000 births (15).

The annual incidence of infant HCP in sub-Saharan Africa is unknown. The burden of infant HCP in East Africa is significant, with more than 6000 new cases estimated per year. The majority is caused by neonatal infection. The experience from CURE Children's Hospital of Uganda (CCHU) has demonstrated infant HCP to be the most common pediatric neurosurgical problem presenting for treatment in East Africa.

The causes of HCP in these children, and the ability to treat it, are seriously impacted in an environment characterized by poverty, poor infrastructure, and unstable politics (3).

In Ethiopia, the etiology and incidence rates of HCP can be assumed to correspond to what has been reported from other East African countries (5). According to extrapolated estimates from Uganda (3), there will be approximately 6,000 new cases per year in East Africa and if these estimates are also valid for Ethiopia, one can expect between 2,000 and 4,000 new cases of pediatric HCP per year (5).

2.3. Types of HCP

HCP is caused by a variety of medical problems including birth defects, in utero infections, and malformations within the brain. If HCP is present before or at birth, it is called congenital HCP. Many cases of congenital HCP are thought to be caused by a complex interaction of genetic and environmental factors. When HCP develops after birth and is caused by a factor such as head injury, meningitis, or a brain tumor, it is termed acquired HCP (14). However, forces such as hemorrhage and infection can act prenatally and also cause "congenital" HCP. Moreover, some genetic forms of HCP are not evident at birth but develop over time (16).

It was reported in three African countries, Zambia, Zimbabwe, and Malawi, the most common cause of congenital HCP were associated with the neural tube defects (NTDs) of Encephaloceles and Meningomyelocele (MMC) and with Aqueductal stenosis. Postmeningitic HCP comes next in frequency. In Zambia, there is a special recognition of hemorrhagic HCP. In these countries, few cases of HCP associated with neoplasms have been reported (17).

HCP secondary to CNS infection is the single most common cause of HCP in Uganda, accounting for 60% of cases (6). Causes and symptoms of HCP are changing with the patient's age. The most common reason for HCP in children before two years of age is intraventricular hemorrhage in the perinatal period whereas in children older than two years is an inflammatory process (18).

2.4. Risk Factors Associated with Pediatric HCP

A 10-year retrospective study done on 596 well-defined cases of congenital HCP patients treated at the University of Mississippi Medical Center was able to identify several significant risk factors. The identified risk factors included lack of prenatal care, multiparous gestation, maternal diabetes,

maternal chronic hypertension, and maternal hypertension during gestation and alcohol use during pregnancy. This study showed that several key risk factors were identified to be strongly associated with the development of congenital HCP in an infant. The prevalence of familial patterns of inheritance for congenital HCP suggests a broader role for genetic factors in the pathogenesis of congenital HCP (9). Environmental factors, such as infection and drugs cause 7% to 10% of congenital anomalies. Although the human embryo is well protected in the uterus, environmental agents-teratogens-may cause developmental disruptions after maternal exposure to them. Teratogen is any agent that can produce a congenital anomaly or increase the incidence of an anomaly in the population and may produce mental retardation during the embryonic and fetal periods (19).

Infection with cytomegalovirus (CMV) is the most common viral infection of the fetus. Newborn infants infected during the early fetal period usually show no clinical signs and are identified through screening programs. CMV infection later in pregnancy may result in severe anomalies: Intrauterine growth restriction (IUGR), HCP, and cerebral palsy. The Toxoplasmosis Gondi organism crosses the placental membrane and infects the fetus causing destructive changes in the brain (intracranial calcifications) that result in mental deficiency, microcephaly, and HCP. Mothers of congenitally defective infants are often unaware of having had toxoplasmosis. Primary maternal infections (acquired during pregnancy) of congenital syphilis nearly always cause serious fetal infection and congenital anomalies; however, adequate treatment of the mother kills the organism, thereby preventing it from crossing the placental membrane and infecting the fetus. Early fetal manifestations of untreated maternal syphilis are congenital deafness, abnormal teeth and bones, HCP, and mental retardation (19).

2.5. Diagnosis of HCP

The diagnosis of HCP is based on a correlation between clinical symptoms of elevated intracranial pressure and the image of the dilated ventricular system. The types of HCP: communicating and non-communicating with subarachnoid space, and the diagnosis depend on CT and MR images (18) . MRI imaging is the premier imaging modality for diagnosing the various forms and causes of HCP. MRI imaging is also sensitive to the presence of deep white matter ischemia that may contribute to the cause of the idiopathic form of normal-pressure hydrocephalus (NPH). Although CT is satisfactory for imaging in the axial plane, MRI imaging is capable of imaging in any plane

to better demonstrate any cause of observation. MRI imaging is also more sensitive than CT to interstitial edema (trans-ependymal flow of CSF) and the hyper-dynamic CSF flows seen with shunt-responsive NPH. On sagittal MR images, we can measure the distance between mammillary bodies and the brainstem or the size of recesses of the third ventricle (20). Imaging examinations make possible both diagnosis and establishing causes of HCP. Performing CT examination or MRI we can estimate the degree of ventricular system dilatation (21). Imaging examinations differentiate the normal pressure and elevated intracranial pressure (ICP) HCP (22). Brain sonography has emerged as an effective tool in diagnosing progressive ventricle dilation and may be used for continuous follow-up. It is also used as a neuroimaging modality to assess the brain before conducting surgery for ETV shunt and catheter placement. It also provides adequate information about cortical thickness (23).

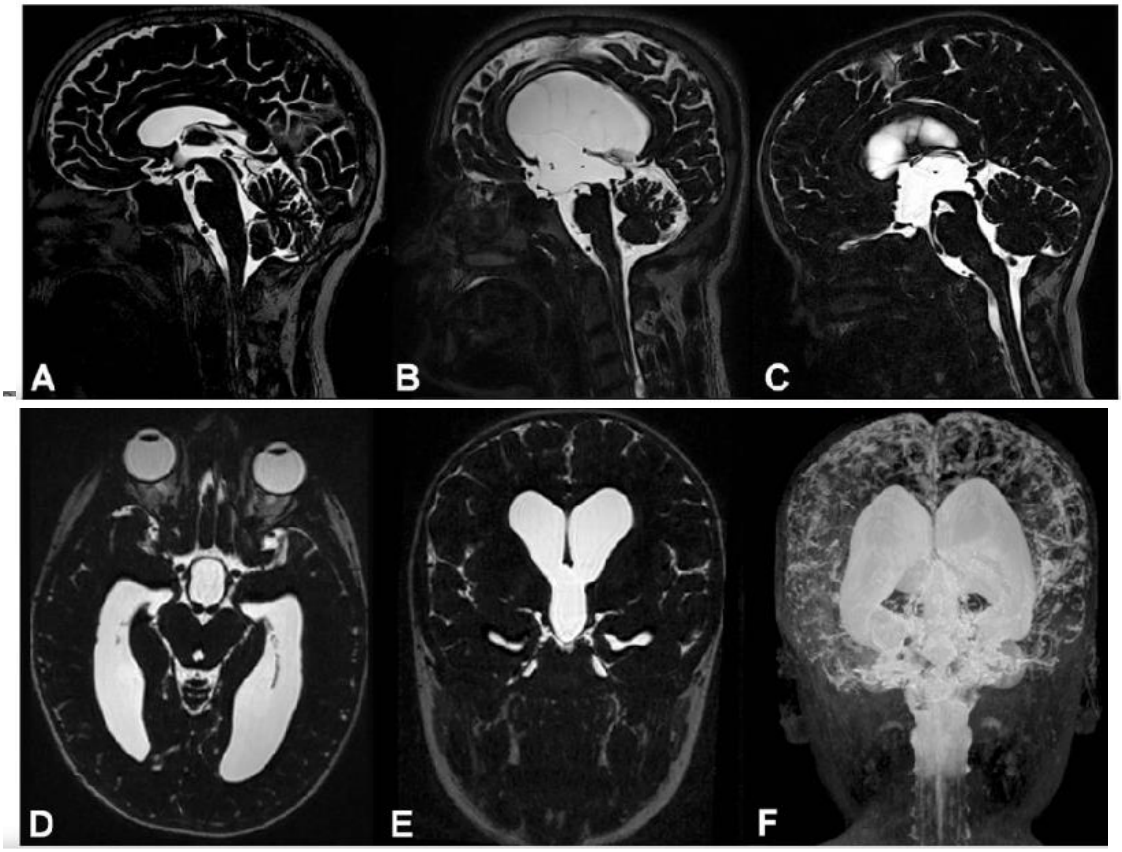
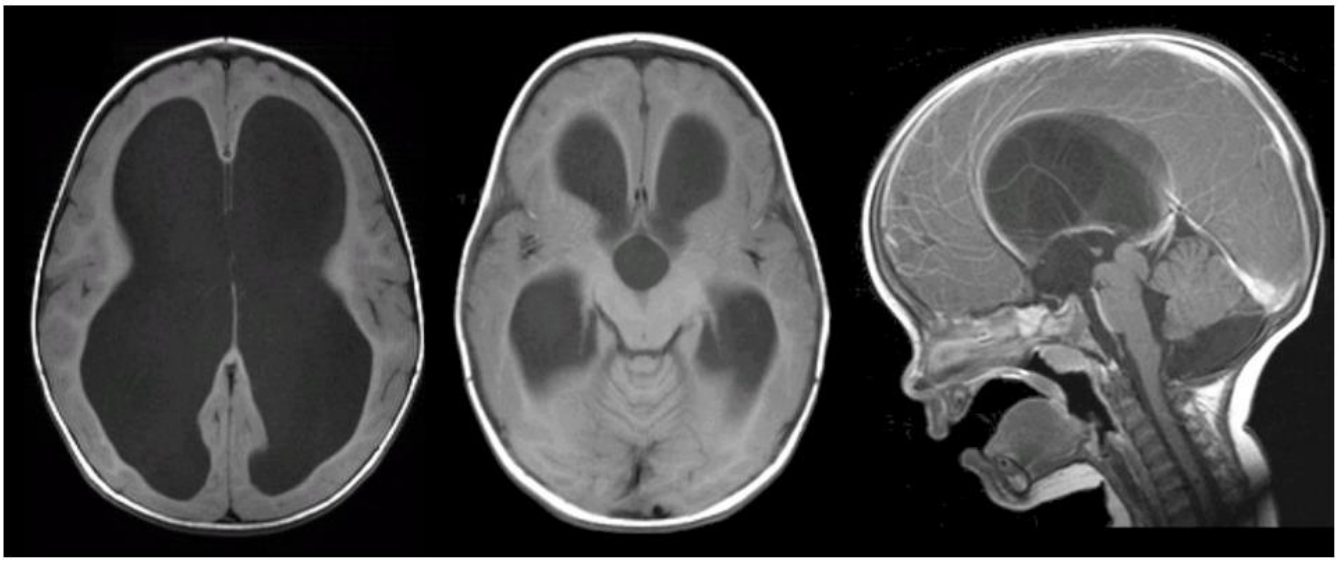


Fig. 1- Heavily T2W 3D-SPACE images of different cases. A normal midline sagittal image is shown for comparison (A). The rest of the images from two different patients with aqueductal stenosis demonstrate enlargement of the ventricles proximal to the obstruction (B, C), enlargement of the third ventricular recesses (B, C), dilated ventricular horns (D–F), and narrowed cortical sulci (maximum intensity –MIP- image, E), which are typical findings of obstructive hydrocephalus. (24)



A 3 year-old girl presented with an enlarging head circumference in association with headaches and an altered gait. On examination, she had papilledema, impaired upgaze, and bilateral lid retraction.

Fig. 2- Non-Communicating Hydrocephalus: (Left and Middle) T1-weighted axial MRIs; (Right) T1-weighted with gadolinium sagittal MRI. Note the massive enlargement of the lateral ventricles. In addition, the third ventricle is markedly enlarged and has assumed a circular shape, as opposed to the normal slit appearance. The cause of the hydrocephalus can be seen on the sagittal MRI scan - there is compression of the cerebral aqueduct by an enlarged tectum of the midbrain (i.e., the quadrigeminal plate). Subsequent biopsy demonstrated a low-grade glioma.

(From https://case.edu/med/neurology/NR/NonCommunicatingas3.htm)

2.6. Treatments, treatment failures and complications of HCP

HCP treatment is based on two surgical methods; VP shunt insertion in the case of communicating HCP and ETV in the case of non-communicating HCP (25). The most often place of ventriculostomy is perforation of the floor of the third ventricle just anterior to the maxillary bodies (26). It makes a possible gradual decrease in the size of the ventricles. Imaging examinations are performed to control shunt function or ventriculostomy condition (27). Insertion of the ventricular shunt may result in large numbers of complications which present within six months from surgery. The overall rate of shunt malfunction is 40% for patients before the age of two and 30% in the older age group (28). Shunt failure is the most common indication for re-operation and occurs frequently, both in developed countries and low-income countries. Proximal shunt obstruction due to ventricular catheter occlusion or misplaced ventricular catheter appears to be the most common cause of shunt failure (11). These complications can concern both shunt tips; intracranial and distal shunt catheters (29).

The most severe complication of ventricular tip insertion is intracranial hemorrhage as a result of the procedure or rapid decompression of the ventricular system. Chronic shunt placement can cause Craniosynostosis in the youngest children with separated sutures. A slit ventricle syndrome can become a problem in a small subset of 1% to 5% of older children chronically shunted (30). These patients present symptoms of intracranial hypertension although they have small ventricles in CT findings. Another complication in shunted patients with non-communicating HCP is the isolated fourth ventricle (31). According to a Norwegian study, the incidence of infections was significantly correlated with age, type of operation, and etiology of HCP: infections being common during the first 6 months of life, following primary shunt insertions rather than revisions, and in children with MMC related HCP (32). Among other possible factors that are related to shunt infection is a poor condition of the skin, presence of intercurrent infection at the time of surgery, prolonged operation time, as well as the education and experience of the neurosurgeon (32-36).

2.7. Management of HCP

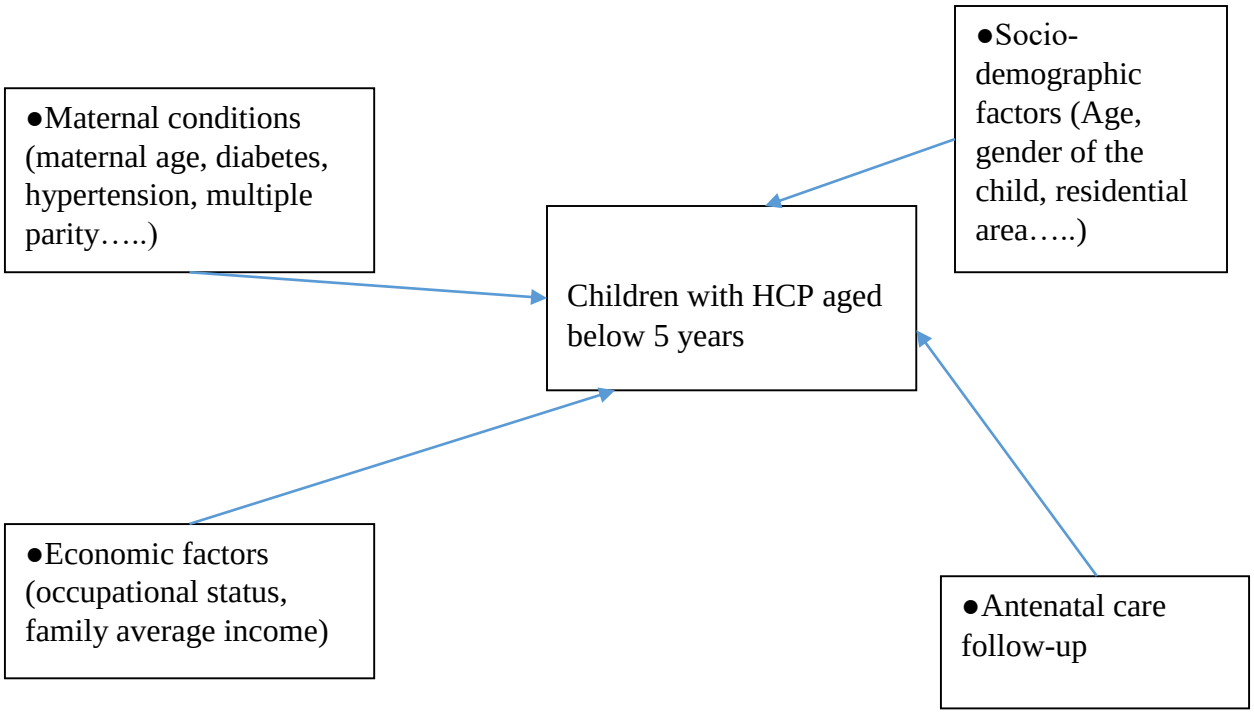
Management of HCP in the developing world poses the greatest challenge mainly due to the limited resources that are available and the scarcity of trained neurosurgeons. The high cost of shunts used to be a major obstacle for the management of HCP until recent years. This problem

was tackled in Ethiopia and other African countries by the introduction of the relatively cheap Chhabra shunt (37). It has been shown that there is no difference in outcome between the Chhabra shunt and the much more expensive shunts commonly used in the Western world (38).

HCP is a treatable condition that when left untreated, has devastating or fatal consequences. In Africa, the problem should be addressed on three fronts: prevention, development of competent treatment centers, and public education. Efforts to determine the bacterial etiology of PIH will be crucial to identify the chief times and modes of transmission as well as the common infecting organisms. Continued research and education are essential if a significant reduction in morbidity and mortality from this disease is to be accomplished (3).

2.8. Conceptual/Theoretical framework

Several key risk factors prevalence of familial patterns, lack of prenatal care, multiparous gestation, maternal diabetes have been identified to be strongly associated with the development of HCP in an infant (9). This study has used the following independent variables to assess associated risk factors of HCP.


●Socio-demographic factors (Age, gender of the child, residential area…..)
●Maternal conditions (maternal age, diabetes, hypertension, multiple parity…..)
Children with HCP aged below 5 years
●Economic factors (occupational status, family average income)
●Antenatal care follow-up

3. RESEARCH OBJECTIVES

3.1. General Objectives

The general objective of this study is to assess pediatric HCP prevalence and associated risk factors from selected diagnostic centers in Addis Ababa, Ethiopia.

3.2. Specific Objectives

- To assess the prevalence of pediatric HCP in selected diagnostic centers in Addis Ababa, Ethiopia
- To identify risk factors and their association with HCP in selected diagnostic centers in Addis Ababa, Ethiopia

4. METHODOLOGY

4.1. Study Setting and Period

This study was performed in four of the diagnostic centers that work in close association with Addis Ababa University, Wudassie Diagnostic Center (WDC), Dr.Alia Diagnostic Center, Pioneer Diagnostic Center, and BMY Diagnostic Center. These diagnostic centers were selected randomly. This study was conducted from January 2018 to February 2020.

In Addis Ababa, Ethiopia, within the private sector, eight diagnostic centers provide imaging services that include MRI and CT. Four private hospitals provide these same services. Though there are ten public hospitals in the capital, these services are now limited to three.

Founded in 2008, Wudassie Diagnostic Center (WDC) is one of the diagnostic centers with MRI, CT scan Digital X-ray, and Ultrasound service in the country. This center has a surplus flow of patients admitted to its Radiology unit for diagnostic purposes. In regards to personal composition, the center has four Radiographers, five Radiology Technologists, two Radiologists, and ten Nurses as health professionals that drive the workforce within the MRI and CT imaging unit. This unit scans about 100 patients per week. Out of these 100 patients, 30 are pediatric patients; of these pediatric patients, 10 are pediatric patients with HCP (personal communication).

4.2. Study Design

A cross-sectional facility-based study was conducted over a two-time period, i.e. a 2-year retrospective data collection from January 2018 to January 2020 and a prospective data collection from May 2019 to February 2020. The study design involved children aged 5 years and below who came to the selected diagnostic centers during the data collection periods.

4.3. Source Population

The source population was all pediatrics aged 5 years and below who came to the **diagnostic centers associated with Addis Ababa University in Addis Ababa**, **Ethiopia** during the data collection periods.

4.4. Study Population

The study population was pediatrics aged 5 years and below who came for **MRI /CT examination to the selected diagnostic centers** during the data collection periods.

4.5. Sample Size and Sampling Technique

The 2-year retrospective data collection made from January 2018 to January 2020 yielded 1,101 patients. A prospective data collection made from May 2019 to February 2020 yielded 99 patients. This study involved all children aged 5 years and below who came to the selected diagnostic centers during the data collection period.

All pediatric patients who were admitted for MRI and CT examination during the time of data collection and those who were included in as part of the inclusion criteria from whom consent had been taken were studied. A cross-sectional facility-based study was utilized in which all children below 5 years who had MRI and CT evaluation in the period of January 2018 to February 2020 were included in the study.

4.6. Inclusion and Exclusion criteria

As the majority of children who present with HCP do so before 2 years of age (39, 40), this study has tried to include those under 5 years of age.

4.6.1. Inclusion Criteria

- All children of either gender aged 5 years and below admitted for MRI /CT examination of the Brain during the data collection periods
- Those parents/caretaker willing to participate in the study

4.6.2. Exclusion Criteria

- Patients, who had surgical procedures for HCP before the study period started
- Patients, under 5 years but who had imaging examination besides Brain were excluded
- Parents/caretaker not willing to participate in the study
- Those parents/caretaker unable to communicate for some reason and patients who were critically ill were excluded

4.7. Variables

4.7.1. Independent Variable

- Socio-demographic factors (Age and gender of the child, educational level of parents and caregivers, residential area)
- Economic factors (occupational status, family average income)
- Maternal conditions (maternal age, diabetes, hypertension, multiple parity, alcohol, tobacco, and drug abuse; infection rates and trauma during pregnancy)
- Antenatal care follow-up (folic acid supplement consumption, prenatal care given)

4.7.2. Dependent Variables

Children with HCP aged below 5 years

4.8. Operational Definition

Depending on Radiographic investigations, it was classified as **Non-communicating (Obstructive**), i.e. if the 4th ventricle was not enlarged and **Communicating (Non-obstructive)** if all four ventricles were enlarged (5).

16-Slice CT: CT scanner which took 16 cross-sectional images and places them on top of one another creating an accurate representation of patient's tissues, organs, and bones with faster scanning time. This study applied standard axial scanning technique with a slice thickness of **3mm, kV (kilovoltage) of 120, and mAs (milliampere seconds) of 300** for head scans of the children to diagnose HCP.

MRI scanner (0.35T Strength): tomographic imaging modality that produces three-dimensional images consisting of individual slices of the brain. It uses a high magnetic field that can be measured outside of the body and used to generate very high-resolution diagnostic images that reveal information about water molecules in the brain and their local environment. The image was displayed in all three planes, i.e., axial, coronal, and sagittal. Imaging sequences of **T2 weighted-turbo spin echo-transverse, T1weighted-spin echo-transverse, T2weighted FLAIR-coronal-dark fluid, T2weighted-turbo spin echo-sagittal, T1weighted-STIR-transverse, diffusion weighted-180^0** and **5mm slice thickness** were applied during the scanning period.

4.9. Data Collection Instrument

Parents/caretakers of children who came to the selected diagnostic centers for MRI/CT examination were informed about the study. Pre-tested semi-structured questionnaires were used for data collection. The data collection tool, survey instrument, was prepared in English – after passing through rigorous revision and pre-test in a real study location. Aiming to simplify the data collection, a standard translation was made into Amharic, and consistency was checked with the English version during the data checking. The questionnaire consisted of socio-demographic, economic factors, and maternal conditions of the study participants. Brain images were acquired using Philips Medical Systems 16-Slice CT and Magnetom- Siemens 0.35T strength MRI scanner with standard brain receiving coils. Images were acquired using standard scanning techniques. Finally, neuroimaging findings were extracted from reports done and signed by senior consultant Radiologists and Neuro-Radiologists. CT and MRI imaging and clinical data records were retrieved and recorded in a format designed to include patients' sex, age, clinical indication, and imaging finding.

4.10. Data Collection Procedure

The retrospective data were collected by the employment of a checklist that included the patient's clinical indication, the type of modality used, confirmation of HCP, and type of HCP confirmed. The checklist also included the name of the diagnostic center and the time at which the data was collected. The prospective data were collected through a pre-tested semi-structured questionnaire. The questionnaire consisted of socio-demographic and economic factors, maternal conditions, and radiological results of the study participants. Both the retrospective and prospective data were collected by nurses (BSc in Nursing) within each diagnostic center and they were employed by the principal investigator.

4.11. Data Quality Control

One day training along with the demonstration of data collection tools was prepared by the principal investigator for all data collectors. The training focused on the objective of the study, confidentiality, consenting procedures, interviewing skill, and description of each variable. The questionnaire was originally prepared first in English then translated into Amharic and then back to English to maintain its consistency. To ensure the validity and reliability of the tools, impartial personnel, Public Health expert was used; supervision was also carried out by the principal

investigator to check completeness and consistency to keep the quality of the data. The questionnaire was pre-tested on 12-pediatrics. Based on the pretest, questions were revised, edited, and those found to be unclear or confusing were removed.

4.12. Data Analysis

The data were entered, cleaned, and analyzed using SPSS software version 23.0. The data collected was analyzed by descriptive analysis. As binary logistic regression estimates the relationship between one or more variables, a bivariate analysis was applied along with a 95% confidence interval (CI) to test the degree of association between dependent and independent variables. Multivariate analysis was applied to identify predictors of the outcome variable. A P-value of less than 0.05 was taken as statistically significant.

4.13. Ethical Consideration

Ethical clearance was obtained from the postgraduate office of Anatomy, College of Health Sciences; Addis Ababa University. Permission was obtained from the office of selected diagnostic centers. The purpose and importance of the study were explained to each study participant and they were informed that no personal identifiers were used in the data. Verbal and written consent was also obtained from each participant. Participants had the right to be excluded from the study if they were not voluntary to participate.

4.14. Dissemination and Utilization of Results

The findings of this study will be presented to the Department of Anatomy and Department of Medical Radiology Technology (MRT), College of Health Sciences, Addis Ababa University. The results will also be disseminated through publication in local or international journals, presentations on annual scientific seminars, conferences, and meetings.

5. RESULTS

This study identified pediatric HCP patients and their associated risk factors conducted over two periods. A 2-year retrospective data collection (January 2018-January, 2020) yielded a total of 1,101 patients and prospective data collection yielded a total of 99 patients (May 2019-February 2020)

In the retrospective study, 639(58%) males and 462(42%) females participated. Their age ranged from 1 to 60 months with a mean age of 22.3 months and a standard deviation of ±18.8. There were 753 (68.4%) children aged younger than 24 months (Table 1). Fifty-seven (57.6%) males and 42(42.4%) females were included in the prospective study with their age ranging from 1 to 60 months; with a mean age of 24.9 months and a standard deviation of ±19.2. This data set had 60 (60.6%) children aged younger than 24 months (Table 2).

The prevalence of HCP was calculated separately for both study periods. The number of children diagnosed with HCP during the retrospective study was 245 (22.3%) and of these HCP cases, 153(62.4%) were classified as non-communicating HCP and 93(37.9%) as communicating HCP based on MRI and CT images (Fig.2). Males were relatively higher to be diagnosed with HCP in this study (140 patients accounting for 57.14% of all patients diagnosed with HCP).

Prevalence of HCP calculated during the prospective study was 23 (23.2%) and of these HCP cases, 13(56.5%) were classified as non-communicating HCP and 10(43.5%) as communicating HCP based on MRI and CT images (Fig. 4). Females had a relatively higher chance of being diagnosed with HCP in this study (12 patients accounting for 52.17% of all patients diagnosed with HCP).

5.1. Characteristics of Study Participants of the Retrospective Study

This retrospective study included a total of 1,101 pediatric patients. Out of these, 639(58%) were males and 462(42%) were females. Their age ranged from 1 to 60 months with a mean age of 22.3 months and a standard deviation of ±18.8. These pediatric patients underwent MRI and CT imaging investigations. MRI was used to image 736(66.8%) and 365(33.2%) were imaged using a CT machine.

Table 1. Characteristics of Study Participants of the Retrospective Study within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020

Variable	Category	Frequency	Percent (%)
Age of child	≤24 months	753	68.4
	≥24 months	348	31.6
Gender	Male	639	58
	Female	462	42
Type of modality used	MRI	736	66.8
	CT	365	33.2

5.2. Characteristics of Study Participants of the Prospective Study

This prospective study included a total of 99 pediatric patients. Out of these, 57(57.6%) were males and 42(42.4%) were females. Their age ranged from 1 to 60 months with a mean age of 24.9 months and a standard deviation of ±19.2. Sixty (60.6%) children were aged younger than 24 months These pediatric patients underwent MRI and CT imaging investigations. Ninety-three (93.9) were imaged using MRI and 6(6.1%) were imaged using CT.

Regarding the maternal history, those aged 18-23 were 23 (23.7%), those aged 24-29 were 45 (46.4%), those aged 29-34 were 17 (17.5%), and those aged 35-40 were 12 (12.4%). Concerning the mother's educational level, those that did not attend school were 22(24.2%), on the other hand, those who attended elementary school we 29 (31.9%), those that went to high school were 22(24.2%) and those that had a diploma and above were 18(19.8%).

Forty-nine (49.5%) of the mothers interviewed were from the rural area and 74 (81.3%) were housewives. Seventy-five (82.4%) of the mothers reported that they attended the antenatal clinic during the pregnancy, 29 (32.2%) did not take their folic acid nutritional supplement, 58 (58.6) started consuming the folic supplement after conceiving, and 54 (58.7%) of them were scanned by Ultrasound during their prenatal follow-up visits. The majority of these mothers had vaginal delivery 71 (78.0%) as opposed to 19 (20.9%) of Caesarean deliveries.

History of HCP among families was found to account for 46 (46.5%) of all the interviewed cases. Also, it was identified that 55.6% of the families had a first-degree relative and 22.2% had second and third-degree relatives with HCP. (Table 2)

Table 2. Characteristics of Study Participants of the Prospective Study within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020

Variables	Category	Frequency	Percent (%)
Age of child	≤24 months	60	60.6
	≥24 months	39	39.4
Gender	Male	57	57.6
	Female	42	42.4
Age of mother	18-23	23	23.7
	24-29	45	46.4
	29-34	17	17.5
	35-40	12	12.4
	Did not attend school	22	24.2
The educational level of the mother	Elementary school(1-8)	29	31.9
	High school(9-12)	22	24.2
	Diploma and above	18	19.8
	Employed	17	18.7
Occupational status of the mother	Housewife	74	81.3
Type of modality used	MRI	93	93.9
	CT	6	6.1
Residential area	Urban	50	50.5
	Rural	49	49.5
Antenatal care follow up	Yes	75	82.4
	No	16	17.6
Mode of delivery	Cesarean	19	20.9
	Vaginal	71	78.0
Trauma during pregnancy	Yes	8	8.8
	No	83	91.2
Pre-eclampsia	Yes	9	9.9
	No	82	90.1
Sexually transmitted disease	Yes	4	4.4
	No	87	95.6
Diabetes mellitus	Yes	2	2.2
	No	89	97.8
Uterine infection	Yes	9	9.9
	No	82	90.1
Folic acid supplement	Yes	61	67.8
	No	29	32.2
Usage of folic acid	Before conceiving	3	3.3
	After conceiving	58	58.6
History of HCP	Yes	46	46.5
	No	53	53.5

5.3. Prevalence and Types of Pediatric HCP from Retrospective Study

The number of pediatric patients diagnosed with HCP was 245 (22.3%) based on MRI and CT images. The observed prevalence in the population studied during this study period was 222.72 per 1,000 births. HCP types were classified as non-communicating HCP 153(62.4%), and 93(37.9%) communicating HCP; also based on MRI and CT images.

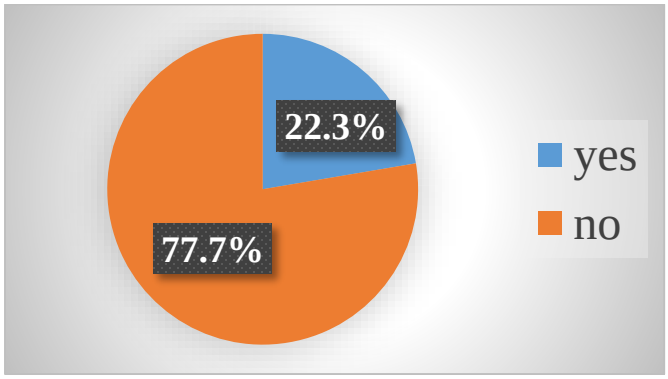


Figure 3. Pediatric HCP cases confirmed by Radiologist within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020

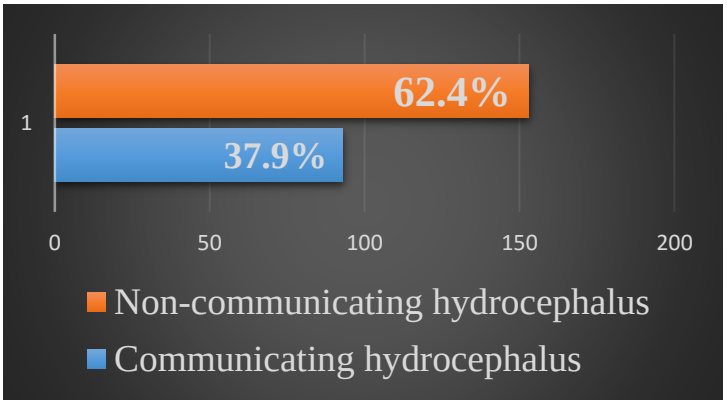


Figure 4.Type of Hydrocephalus confirmed by Radiologist within the selected diagnostic centers in Addis Ababa, Ethiopia, 2018-2020

5.4. Prevalence and Types of Pediatric HCP from the Prospective Study

The number of pediatric patients diagnosed with HCP was 23 (23.2%) based on MRI and CT images. The prevalence observed in the population during this study period is 232.3 per 1,000 live births. HCP types were classified as non-communicating HCP 13(56.5%) and 10(43.5%) as communicating HCP; also based on MRI and CT images.

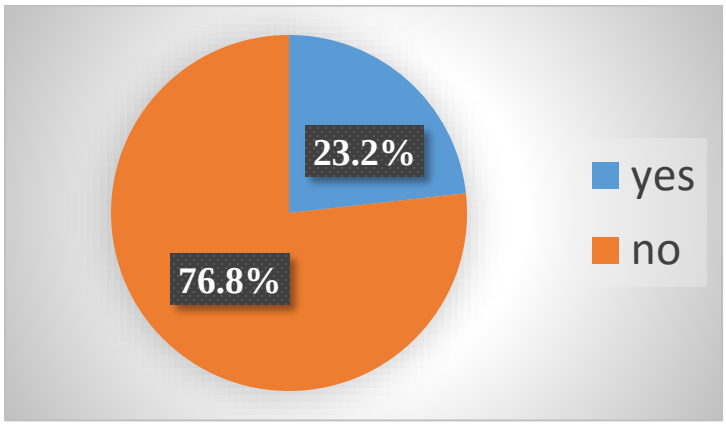


Figure 5.Hydrocephalus confirmed by Radiologist within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020

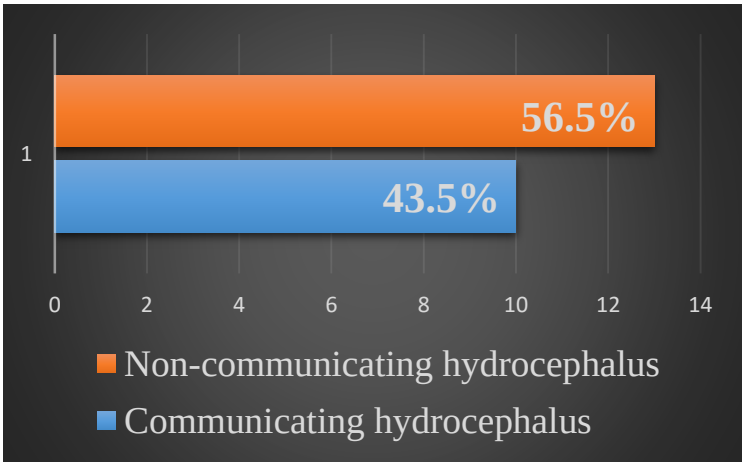


Figure 6. Type of Hydrocephalus confirmed by Radiologist within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020

5.5. Risk Factors Associated with HCP in the Retrospective Study

The risk factors associated with pediatric HCP were also calculated separately for the two study periods. The retrospective study identified 753 (68.4%) children were younger than 24 months; accounting for the majority. With a statistical significance of (AOR=1.90 [95% CI= 1.36, 2.26], P<0.05), the study has found that out of all patients diagnosed with HCP, 192 (78.3%) infants were younger than 24 months; accounting for the majority of the HCP patients. (Table 3)

Table 3. Associated Risk factors of HCP of the Retrospective Data within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020

Variables	**Category**	**Diagnosis**		**COR (CI 95%)**	**AOR (CI 95%)**
Variable		Diagnosis		COR (CI 95%)	AOR (CI 95%)
		Yes	No		
Age of the child	≥24 months	53	293	1	1
	≤24 months	192	559	1.89 (1.36, 2.65)*	1.90 (1.36, 2.26)*
Gender	Male	140	497	1	1
	Female	105	355	0.95(0.72, 1.27)	1.01 (0.75, 1.35)

Note: *significance; p<0.05

5.6. Risk Factors Associated with HCP in the Prospective Study

The prospective study identified the majority of children 60 (60.6%) were younger than 24 months. Out of all patients diagnosed with HCP, 15 (65.2%) infants were younger than 24 months; though this accounted for the majority of the HCP patients, it was not found to have statistical significance (P>0.05). No statistical significance was identified among the gender of these patients either (P>0.05). (Table 4)

Mothers who did not take folic acid nutritional supplements were 29 (32.8%). These mothers were identified to be significantly associated with HCP occurrence (OR=6.107 [95% CI=1.32, 28.35], P<0.05). Concerning the utilization of supplements only once after they found out they were pregnant, there is a significant association of HCP development at P<0.05 with a proportion of 58 (58.6%) (Table 4)

History of HCP among families was found to account for 17 (73.9%) from all the confirmed cases of HCP. Also, of all the confirmed cases of HCP, it was identified that 8.69% of these families had a first degree relative with HCP. History of HCP was found to have a significant association with the occurrence of HCP (OR=4.52 [95% CI=1.624- 12.984], P<0.05). (Table 4)

The interviewed mother's age was grouped into four categories. This category included mothers aged 18-23 (23.7%), 24-29 (46.4%), 29-34 (17.5%), and 35-40 (12.4%). No significant association was found among any of these categories (P>0.05).

The interviewed mother's educational level was also grouped into four categories. This category included mothers who did not attend school (24.2%), those that went to elementary school (31.9%), those that went to high school (24.2%), and those that had a diploma and above (19.8%). A significant association was not found among any of these categories (P>0.05).

The majority of mothers 75(82.4%) attended their antenatal clinic follow-ups. This study indicated that 17.6% of mothers had not gone to their check-ups; statistical significance, nevertheless, was not reached among these mothers (P>0.05).

During the interview process, mothers that did not experience trauma were 83 (91.2%). However, this study indicated that 17.3% of mothers of children with HCP suffered from a trauma during their gestation, as there is no statistical significance of such (P>0.05).

This study identified that interviewed mothers who had Pre-eclampsia were (9.9%), chronic hypertension (8.8%), and Diabetes mellitus (2.2%) during their gestation. Though these variables were studied as risk factors, a significant association with HCP was not found (P>0.05). Sexually transmitted infections were identified among 4.4% of the interviewed mothers but this did not reach significance (P>0.05). This study also did not find any association between the use of alcohol and cigarette smoking among mothers interviewed (P>0.05). This study identified that mothers who took medication (prescribed or otherwise) were (10.1%) and these mothers that took this medication in the first-trimester were (33.3%), the second trimester was (55.6%) and in the third trimester were (11.1%); however, this did not reach statistical significance (P>0.05)

Table 4. Associated Risk factors of HCP of the Prospective data within the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020.

Variables	Category	Diagnosis		COR (CI 95%)	AOR (CI 95%)
Age of child		Yes	No		
	≥24months	8	31	1	1
	≤24 months	15	45	1.2(0.08, 1.3)	1.3 (0.6, 1.7)
Gender	Male	11	46	1	1
	Female	12	30	0.59(0.23, 1.52)	1.69 (0.63, 4.54)
Age of mother	18-23	2	21	1	1
	24-29	14	31	0.21(0.04, 1.03)	0.22 (0.04, 1.08)
	29-34	5	12	0.23 (0.038, 1.36)	0.24 (0.04, 1.43)
	35-40	2	10	0.48(0.06, 3.88)	0.43 (0.05, 3.58)
The educational level of the mother	Did not attend school	8	14	1	1
	Elementary school(1-8)	6	23	2.2(0.63,7.64)	2.04 (0.54, 7.79)
	High school(9-12)	4	18	2.6(0.64,10.31)	2.61 (0.57, 11.7)
	Diploma and above	3	15	2.8(0.63 12.9)	3.92 (0.78, 19.5)
Antenatal care attendance	Yes	19	56	1	1
	No	2	14	2.38(0.49, 11.41)	0.34 (0.06, 1.78)
Consumption of folic acid	Yes	19	42	1	1
	No	2	27	6.107(1.32, 28.35)*	1.64 (0.052, 51.5)*
Use of folic acid	Before conceiving	2	1	1	1
	After conceiving	17	41	0.59(0.04, 0.804)*	0.27 (0.009, 8.32)*
History of HCP in the family	Yes	17	29	1	1
	No	6	47	4.52(1.624, 12.984)*	4.89 (0.64, 3.23)*
Trauma to the mother during pregnancy	Yes	4	4	1	1
	No	17	66	3.882(0.88, 17.140)	2.93 (0.56, 15.3)

Note: *significance; P<0.05

5.7. Prevalence of Congenital and Acquired Hydrocephalus

5.7.1. Prevalence of Congenital and Acquired HCP within the Retrospective Study

Prevalence of congenital and acquired HCP in both study periods was studied separately based on MRI and CT images.

Of all children diagnosed with HCP (22.3%), congenital HCP was described in terms of Aqudectal stenosis and NTDs. Aqudectal stenosis, accounting for 17.6%, was identified to be the most prevalent.

NTDs were found as the second most prevalent type of congenital HCP. These NTDs were further studied and explained through Chari II 41(16.7%), and Chari III malformations 1(0.4), Dandy-Walker variant 28(11.4%), and Colpocephaly 8(3.2%). NTDs associated with MMC 2(0.89%), Encephalocele 5(2.04%), and Meningoencephalocele 3(1.2%) were further identified. These NTDs accounted for 35.91% in total. (Table 5)

Acquired HCP was described in terms of Post-infectious, Post-hemorrhagic, Adhesion of Foramen of Monroe, and tumor-related causes.

Post-infectious HCP (PIH) (3.2%), was determined according to the child's clinical indication and CT and MRI imaging findings. MRI images showing areas of hyper-intensity on T2 weighted images with complete ring enhancement were used as evidence to diagnose cerebral and cerebellar abscess. In acute meningitis, leptomeningeal inflammation over the cerebral convexity and in the basal cisterns seen on delayed Gadolinium-enhanced FLAIR sequence was used to diagnose meningitis with TB and pyogenic causes. Imaging features of enhancement of the ventricular wall and hyper-intense ventricular content on diffusion weight sequence on MRI were used to diagnose Ventriculitits. Following these, PIH was thus defined in terms of chronic in-utero infection (TORCH- Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes), Ventriculitis, Cerebral and Cerebellar abscess, and Tuberculoma that led to the development of HCP. Post-meningitis complications (6.9%) due to Pyogenic and Tuberculous causes were also included in this group. (Table 6)

This same technique was applied to diagnose post-hemorrhagic complications leading to HCP as well. The hemorrhagic complications were depicted as marked hypointensity on the Gradient echo (GRE) T2 MRI sequence.

Subdural hematoma (0.4%), hypoxic-ischemic cerebral injury (1.2%), perinatal ischemic insult (1.2%), Cystic Encephalomalacia (0.8%), and Dural venous malformation (0.4%) were investigated and included in this group as well. (Table 8)

Tumor-related HCP was diagnosed according to imaging investigations and was identified in terms of Medulloblastoma-Teratoid Rhabdoid Variant 12(4.8%), Craniophangioma (0.8%), Pineal gland Glioma (0.4%), and Ependymoma (0.4%). (Table 7) Another type of acquired HCP identified in this study was the Adhesion of Foramen of Monroe (0.4%)

Table 5. Congenital Pediatric HCP- Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020

Congenital HCP	n	%
Aqueductal Stenosis	44	17.9
Chari II malformation	41	16.7
Dandy-Walker Malformation	28	11.4
Colpocephaly	8	3.2
Encephalocele	5	2.04
Myelomeningocele	2	0.81
Meningoencephalocele	3	1.2

Table 6. Acquired Pediatric HCP- Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020

Acquired HCP	n	%
Post-infectious (chronic in-utero infection (TORCH), ventriculitis, cerebral and cerebellar abscess, and Tuberculoma)	8	3.2
Post-meningitis (complications due to Pyogenic and Tuberculous)	17	6.9
Adhesion of Foramen of Monroe	1	0.4

Table 7. Tumor Related Pediatric HCP- Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020

Tumors (N=16)	n	**%**
Medulloblastoma	12	4.8
Pineal gland glioma	1	0.4
Ependymoma	1	0.4
Craniopharyngioma	2	0.8

Table 8. Post-hemorrhagic HCP Retrospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2018-2020

Etiology of HCP	n	%
Subdural Hematoma	1	0.4
Hypoxic-ischemic cerebral injury	3	1.2
Perinatal ischemic insult	3	1.2
Cystic Encephalomalacia	2	0.8
Dural venous malformation	1	0.4

5.7.2. Prevalence of Congenital and Acquired HCP within the Prospective Study

This study has also tried to assess the prevalence of congenital and acquired HCP separately similar to the retrospective study; of the total pediatric patients diagnosed with HCP (23.2%).

Congenital HCP was were characterized in terms of Aqudectal stenosis and NTDs. Congenital pediatric HCP identified five different types. Of which, the largest, a little more than a quarter was attributable to aqueductal stenosis (26.1%). This, on the other hand, was followed by NTDs further studied in terms of Dandy-Walker malformation (17.4%), and Chari II malformation (8.7%). HCP associated with MMC (8.69%) and Meningoencephalocele (8.69%) were also included in this category. These NTDs accounted for 43.48% in total. (Table 9)

Acquired HCP, similar to the retrospective study, also identified post-infection related post-meningitis complications, post-hemorrhagic, and tumor-related HCP.

The same diagnosis criteria used in the retrospective study were applied here as well. Post-meningitis complications due to Pyogenic and Tuberculous causes account for (8.69%).

Perinatal hypoxic-ischemic injury and post-perinatal hypoxic-ischemic injury due to Ex-vacuo ventriculomegaly were studied as post-hemorrhagic complications. Ex-vacuo ventriculomegaly was not defined as a type of HCP in this study, but its development due to post-perinatal hypoxic-ischemic cerebral injury (21.7%) and perinatal hypoxic-ischemic cerebral injury (13.04%) was identified and investigated as a post-hemorrhagic complication. This group also included Subdural hematomas (21.7%). (Table 11)

This study has also identified tumor-related HCP and has diagnosed it using results of imaging investigations. Medulloblastoma-Teratoid Rhabdoid Variant, Germinoma, and Craniophangioma each accounting for 8.69% were included in this group. (Table 10)

Table 9. Prevalence of Congenital and Acquired Pediatric HCP- Prospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020

Congenital and Acquired Pediatric HCP	n	%
Aqueductal Stenosis	6	26.1
Dandy-Walker malformation	4	17.4
Chari II Malformation	2	8.7
Meningocele	2	8.69
Meningoencephalocele	2	8.69
Post-meningitis (complications due to Pyogenic and Tuberculous)	2	8.69

Table 10. Tumor Related Pediatric HCP- Prospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020

Tumors	n	%
Medulloblastoma	2	8.69
Germinoma	2	8.69
Craniopharyngioma	2	8.69

Table 11. Post-hemorrhagic HCP- Prospective data compilation from the Selected Diagnostic Centers in Addis Ababa, Ethiopia, 2019-2020

Post-hemorrhagic HCP	**N**	**%**
Subdural Hematoma	5	21.7
Ex-vacuo ventriculomegaly due to Post-perinatal hypoxic-ischemic cerebral injury	5	21.7
Ex-vacuo ventriculomegaly due to perinatal hypoxic-ischemic cerebral injury	3	13.04

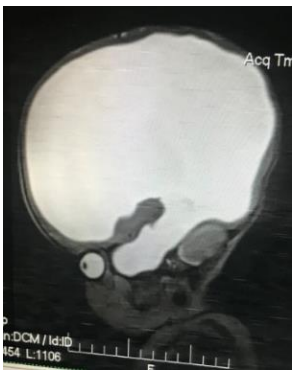
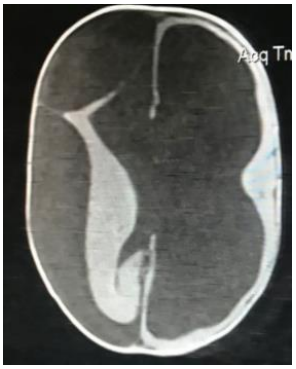
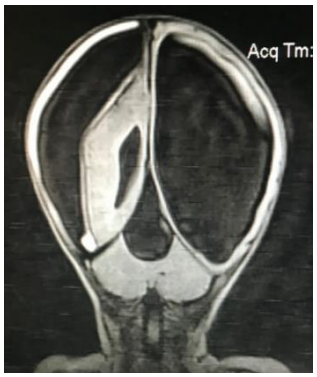
A.  B.  C. 

Fig 7. MRI of a 4 months old male infant represented by A. T2 Sagittal, B. T1 Axial and C. T2 Coronal FLAIR Dark fluid- Finding(s): Superior vermian arachnoid cyst compressing the superior vermix and the tectal plate and effacing the aqueduct causing severe aqueductal stenosis and obstructive HCP. (The image was performed by the assigned Medical Radiology Technologist within the diagnostic center.)

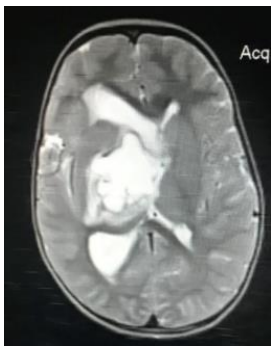
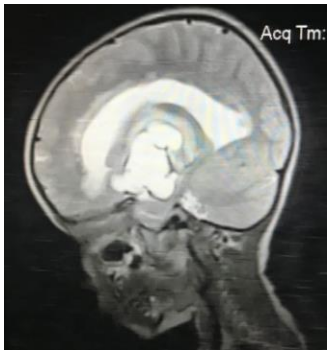
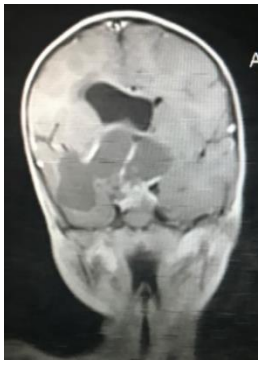
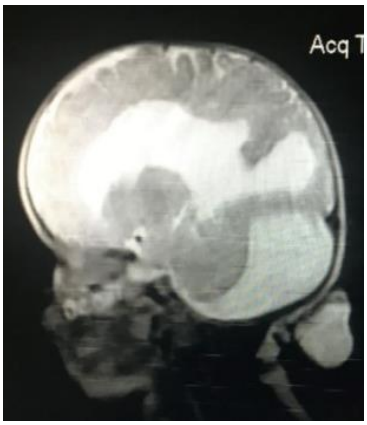
A.  B.  C. 

Fig 8. MRI of a 4 year old male represented by: A. T2 Axial, B. T2 Sagittal and C. T1 Coronal-Post-contrast enhanced sequences. Findings: Extensive cystic supra and right parasella mass with peripheral rim and nodular solid contrast enhancement causing effacement of the third ventricle and left lateral ventricle causing right lateral mono ventricular obstructive severe HCP with subepyndema-predominantly Cystic Craniopharngioma . (The image was performed by the assigned Medical Radiologist Technologist within the diagnostic center.)

A. 

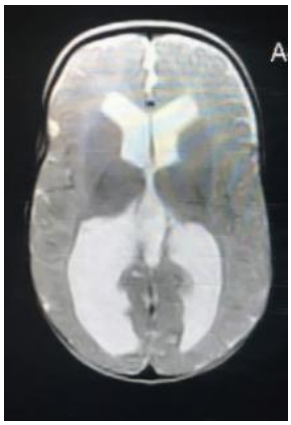
B. 

Fig 9. MRI of a 3 months old female infant represented by A. T2 Sagittal and B. T2 Axial sequences. The image was performed by the assigned Medical Radiologist Technologist within the diagnostic center. Findings- Dandy-Walker huge cyst with Occipital meningocele and HCP

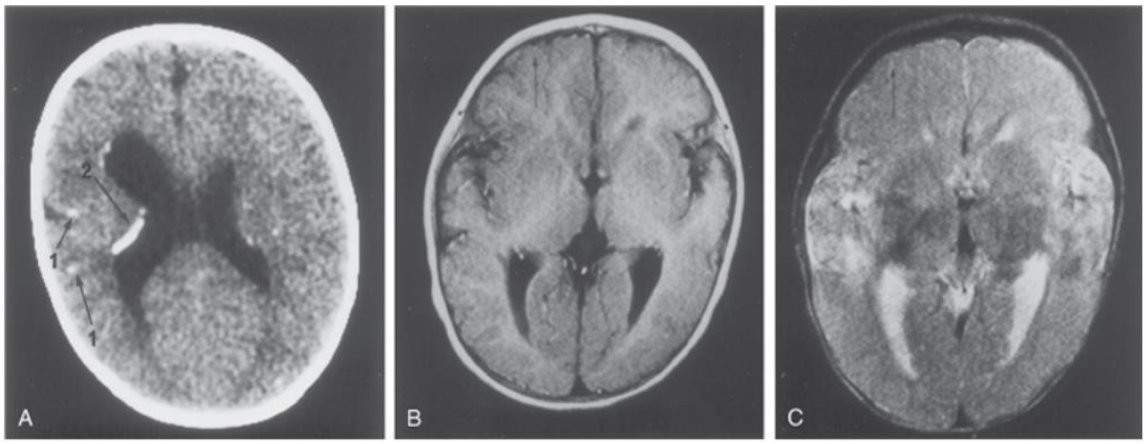


Fig 10. Congenital cerebral anomalies induced by Toxoplasma infection. The diagnostic images were obtained at 2 years and 9 months of age. A Plain computed tomography scan. The lateral ventricles are moderately dilated. Multiple calcified foci are apparent in the brain parenchyma (arrows 1) and along the ventricular wall (arrow 2). B, Magnetic resonance imaging, T1 WI. The cortical gyri are widened on the left side and the cortex is thickened in the left frontal lobe (arrow) compared with the corresponding structure on the right. C, Magnetic resonance imaging, T2 WI. The left frontal lobe shows abnormal hypo-intensity (arrow) (From Moore KL, Persaud TVN, Torchia MG. The developing human: clinically oriented embryology 2020.)

6. DISCUSSIONS

This study was designed to determine the prevalence of pediatric HCP cases and their associated risk factors in Addis Ababa, Ethiopia within two study periods. The age group of pediatric patients ranged from 1 to 60 months. Brain imaging techniques were used to confirm HCP cases.

6.1. Demographics: Sex, Age and Patient Characteristics of both studies

As opposed to their female counterparts, males had a relatively higher chance of being diagnosed with HCP (140 patients accounting for 57.14%). This finding is similar with published studies in other African countries which have shown that the majority of pediatric patients with HCP were males; 64.6% of the population in a study from Tanzania and 53% in a study from Kenya (41); 60.5% in a study from Nigeria (42), as well as a predominance of 51.9% in a study from Uganda (43). The finding also is in agreement with a published study in Ethiopia which similarly found males to be predominant both in isolated HCP (38 male patients accounting for 66.7% of all patients with isolated HCP) and in the MMC associated HCP group (30 male patients accounting for 53.6% of the patients in that group) (5).

However, the prospective study had a different finding; as it was found that females had a relatively higher chance of being diagnosed with HCP (12 patients accounting for 52.17% of all patients diagnosed with HCP). In this study, sex was not considered as one of the risk factors of HCP. As a result, the relatively higher prevalence of HCP among males in retrospective study and females in prospective studies was not further investigated.

In this study, age distribution ranged from 1 to 60 months; there was a slight increment in the mean age of pediatric patients from 22.3 months to 24.9 months in the two study periods but the difference was not statistically significant. A statistically significant association between age and the development of HCP was found ($P<0.05$), in the retrospective study, among children aged younger than 24 months; 192 infants (78.3%) out of all patients diagnosed with HCP. These infants were observed to have a higher risk of developing HCP 1.9 times as opposed to those aged older than 24months. (Table 3) This is similar to an article published in the journal of the International Society for Pediatric Neurosurgery (ISPN) and the National Organization of Rare Disorders (NORD) both of which reported the majority of children who present with HCP do so before 2 years of age (39, 40).

Non-communicating HCP (obstructive HCP) was predominant in both populations, 62.4% in the retrospective and 56.5% in the prospective study. This is in agreement with the Ethiopian study that also found obstructive HCP to be predominant in two of their study periods, 64.7 % during the first period, and 62.2 % in the second (5).

6.2. Prevalence of HCP

In developed countries, the incidence of congenital HCP is estimated at three to five cases per 1000 live births. Excluding secondary HCP and that associated with Spinal Bifida, the incidence of primary congenital HCP has been estimated at 0.2 to 0.8 per 1000 births (4). This study had a different finding as it identified the prevalence in the population studied during the retrospective study to be 222.72 per 1,000 births (2,222.72 per 10,000 births) and the prevalence observed during the prospective study period to be 232.3 per 1,000 (2,323.2 per 10,000 births).

The observed prevalence of pediatric HCP in both studies is much higher than prevalence rates of 20.3 per 10,000 births seen in northern China (15), 4.65 per 10,000 births in four European regions (44), 11 per 10,000 births in Denmark (45), 5.9 per 10,000 births for California (46), and prevalence of 28.7 per 10,000 births in a region of Nigeria (47).

However, the results of this study are in agreement with the study conducted in Uganda-from CURE Children's Hospital of Uganda (CCHU) which demonstrated infant HCP among 3,684 children. The study estimated the infant HCP prevalence rate between 1,000 and 2,000 cases every year (3). This study is also similar to research conducted here in Addis Ababa, Ethiopia that used the estimates applied in the Ugandan research and presented an estimate between 2,000 and 4,000 new cases of pediatric HCP per year (5).

As described earlier, this high prevalence rate of HCP in Ethiopia has been attributed to high percentages of Aqucdectal stenosis, NTDs, and a small contribution of post-infectious causes observed in both study periods. In presenting the causes and incidence rates of HCP from East Africa (5), where it served as a reference for Ethiopia, there is a contradiction concerning the cause of HCP.

6.3. Prevalence of Congenital and Acquired HCP

This study has found the prevalence of congenital and acquired HCP for both study periods. It has identified aqueductal stenosis and NTDs associated with congenital HCP; post-infectious, posthemorrhagic, and tumor-related HCP were associated with acquired HCP.

6.3.1. Aqueductal stenosis and Neural tube defects (NTDs)

This study has identified Aqueductal stenosis (17.9%) as the most prevalent type of congenital HCP. Aqueductal stenosis is a narrowing of the aqueduct of Sylvius which blocks the flow of CSF in the ventricular system. The aqueduct of Sylvius, a channel that connects the third to the fourth ventricle, because of its small size, is the most likely place for a blockage of CSF in the ventricular system (48).

Reports that aqueductal stenosis causes the majority of the Obstructive HCP (48), have been reviewed by this study and it similarly has attributed the non-communicating HCP (Obstructive HCP) predominance in both populations, i.e. 62.4% in the retrospective and 56.5% in the prospective study to Aqueductal stenosis.

Following this, NTDs have been identified as the second most prevalent type of congenital HCP. NTDs compiled within the retrospective data were Chari II malformation, Dandy-Walker malformation, and MMC. (Table 5) This result is in agreement with a study conducted in three African countries; Zambia, Zimbabwe, and Malawi, that stated the most common cause of HCP to be congenital, associated with Aqueductal stenosis and NTDs (17). A similar distribution was also found when compiling the prospective data, Aqueductal stenosis accounting for 26.1%, followed by NTDs (Dandy walker malformation, MMC and Chari II malformation) (Table 9)

In contrast, this study differed from the study in Uganda which indicated HCP secondary to CNS infection to be the single most common cause of infant HCP accounting for 60% of cases (6).

This study is also similar to a study from Saudi Arabia which attributed the cause to Spinal dysraphism 39.3% (associated with Spinal Bifida Cystica and Encephalocele) and Aqueductal stenosis 16.4% of infant HCP cases (49), and the study from Kenya which indicated Spinal Bifida as the most common cause of HCP (50).

The results of this study may be explained by the diagnosis of typical characteristics of NTDs and level of obstruction of the cerebral aqueduct on MRI neuroimaging of the children's brain and clinical history acquired during the interview process that was able to show the classic features of HCP, that is, increase in head size, sun-setting eyes, vomiting, and seizures in the patients.

This study also found HCP associated with MMC accounting for 0.81% retrospectively and 8.69% prospectively. This result is different from the Ugandan study which found MMC associated HCP to account for 14% (3). This finding is also contrary to the study conducted here in Ethiopia that found MMC associated HCP among children aged under 5 years to account for 44.5%. This high percentage was attributed to selection bias where these children with MMC were easily diagnosed just after birth (5). This study also differed from the study in Kenya which found MMC (Spinal Bifida) associated HCP to account for 43.4% (50), south-western Saudi Arabian study that found Spinal Bifida Cystica accounting for (95.8%) (49), and the Tanzanian study that reported MMC to account for 16% of their cases (51).

In this study, HCP associated with Encephalocele accounted for 2.04%; which is higher than the Ugandan study which found Encephalocele accounting for 1% from a total of 468 children diagnosed with HCP (6), and higher than similarly conducted Tanzanian study which found it to also account for only 1% (51).

MMC cases were not encountered as much as expected in this study because it was conducted within diagnostic centers and these patients had better chances of being treated in public hospitals since they were detected early and diagnosed clinically; not a lot of imaging investigations were referred out to diagnostic centers. Besides, there is no centrally managed database of the patient's clinical history in public and private health institutes.

6.3.2. Post-infectious HCP (PIH)

Studies in Uganda (3), Tanzania (51), and Kenya (50) have reported PIH prevalence of 57%, 22.4%, and 27.7%. In our study, however, a prevalence of only 10.1% and 8.69% have been observed in the retrospective and prospective study periods respectively. This discrepancy may be explained by differences in methodology. In the Ugandan study, for example, PIH was defined in terms of the absence of HCP at birth, history of febrile illness or seizure preceding the onset of

HCP, and convincing evidence of prior ventriculitis based on imaging or ventriculoscopic findings if the history was unclear (3). In this study, however, PIH was defined in terms of the patient's clinical history and post-natal CT and MRI imaging investigations. It identified PIH as chronic in-utero infection TORCH infections, Ventriculitis, Meningitis, Cerebral and Cerebellar abscess, and Tuberculoma that led to the development of HCP thus defining PIH in terms of post-natal diagnosis.

This study has identified PIH related post-meningitis complications due to Pyogenic and Tuberculous causes accounting for 6.9% and 8.69% within the retrospective and prospective data respectively. In contrast, this study had a lower percentage when compared with the south-western Saudi Arabia study that found post-meningitis causes accounting for 14.8% (49).

Although this study showed a lower percentage, it is in agreement with the study conducted in Uganda which assumed PIH (57%) secondary to neonatal ventriculitis or meningitis as an important cause of HCP throughout East Africa and in other developing nations. This Ugandan study identified meningitis as the most common probable cause of PIH that leads to ventriculitis, cerebral infraction, aqueductal obstruction, and HCP. The infection that preceded the onset of the HCP in these infants occurred within the neonatal period; these infections, i.e. sepsis and meningitis followed likely due to organisms acquired during delivery (6).

This study also agrees with the study conducted in three African countries; Zambia, Zimbabwe, and Malawi, that identified post-meningitic HCP as the most frequent cause next to NTDs and aqueductal stenosis. PIH was reported among 35 (51.5%) Malawian infants (17). A similar study in Kenya was observed to show the same finding where it classified post-meningitis HCP within the PIH group which was again identified as the second most common cause of HCP following Spinal Bifida (50).

6.3.3. HCP secondary to Tumors and Adhesion of Foramen of Monroe

This study has recognized small contributions of HCP secondary to tumors. It found Medulloblastoma- Teratoid Rhabdoid Variant accounting for 4.8%, Craniopharngioma accounting for 0.8%, and Pineal gland Glioma and Ependymoma each accounting for 0.4%. The prospective study also found Medulloblastoma- Teratoid Rhabdoid Variant, Germinoma, and Craniopharngioma each accounting for 8.69%. This study is similar to the study conducted in three

African countries which found few cases of HCP associated with neoplasms (17). This study however was contrary to the study from Tanzania, which reported a 2.4% occurrence of HCP due to tumors (51).

This study found it difficult to compare the prevalence of HCP due to tumors with other literature because exact values were not adequately reported and there was a difference in methodology. For example, the Ugandan study categorized causes HCP as non-post infectious HCP (NIPH) which accounted for 25% in total. This category included congenital causes, i.e. Dandy-Walker malformation and aqueductal stenosis, and those in whom the cause was indeterminate. Although HCP secondary to tumors was included in this group, its exact value was not reported (3). The study from Kenya similarly used this methodology and identified NIPH to account for 15% of the etiologies of HCP. This classification technique included tumor-related HCP, but again its exact amount was not reported (50).

Adhesion of Foramen of Monroe accounted for 0.4% of the cases of HCP this study found, which is much lower when compared with the Tanzanian study that reported atresia of the Foramen of Monroe to account for 7% of the cases (51).

6.3.4. Post-Hemorrhagic HCP

The non-congenital etiologies of acquired infant HCP associated with post-hemorrhagic HCP of prematurity were reported to be the most common cause of HCP in more economically developed countries (3). Nevertheless, the retrospective study has found a small contribution of intraventricular hemorrhage (IVH) in the occurrence of pediatric HCP. HCP caused by post-hemorrhagic complications accounted for 4.0% in total in this study. This result was similar to a small contribution also observed in the study in Uganda which found only one case of IVH that lead to HCP from 468 children with HCP (6). This study was contrary to the Saudi Arabian study which found post-hemorrhagic HCP to account for 8.2% (49).

Unlike the retrospective study, the prospective study has found a higher contribution of IVH to HCP occurrence. It identified HCP caused due to subdural hematomas accounting for 21.7% and these cases were further complicated by the development of subdural and subarachnoid hygromas. Though this study did not classify Ex-vacuo dilation of the ventricular system (ex-vacuo ventriculomegaly) as a type of HCP, it found its occurrence due to perinatal hypoxic-ischemic

injury accounting for 13.04%. This study has categorized these as post-hemorrhagic complications. Although the exact number of occurrences is not mentioned, a study in Zambia gives special recognition to hemorrhagic HCP (17).

The study from South-western Saudiarabia attributed the causes of the intracranial bleeding leading to HCP to, IVH of prematurity, birth asphyxia, disseminated intravascular coagulation (septicemia and heat stroke), and hemorrhagic disease of newborn (49). The study from Saudi was conducted in the only referral hospital for HCP and enough clinical assessment was made to diagnose their patients and identify the exact causes of IVH. This study was however not able to reach the same conclusion as few details about the child's clinical information were attained from mothers during the interview process, minor clinical details were written on request papers sent for imaging investigations, and difficulty in acquiring patient's full medical charts at a diagnostic center level made it hard to identify the exact causes of IVH.

6.4. Imaging investigations

The early diagnosis of HCP in pediatric patients is essential for the management and treatment of this disease. Imaging examinations make possible both diagnosis and establishing causes of HCP. Performing CT examination or MRI we can estimate the degree of ventricular system dilatation (21).

6.4.1. Computed tomography (CT)

CT is one of the tomographic modalities that work by exposing patients to ionizing radiation (52). This study applied standard axial scanning techniques with a slice thickness of 3mm, kV (kilovoltage) of 120, and mAs (milliampere seconds) of 300 for head scans of the pediatric patients to diagnose HCP. This study has found acute cerebral hemorrhage, TORCH infections, and subdural hematomas better demonstrated by CT. Bones were also more clearly demonstrated on CT since it could absorb ionizing radiation due to its high density. Changes within the skull due to Colpocephaly, Scaphocephaly, Craniosynostosis, and Chari II malformation were also better displayed on CT images. The results of this study are in agreement with an article published by the Department of Radiology in Harvard medical school on neonatal brain imaging that also applied these similar scanning techniques and recommended CT to be reserved for large intracranial hemorrhages requiring immediate evacuation and to characterize TORCH infections.

It also reported cerebellar hemorrhage and inter-hemispheric subdural hematoma were better picked by CT imaging (53).

6.4.2. Magnetic resonance imaging (MRI)

MRI is another tomographic imaging modality that functions by the use of magnetic fields instead of ionizing radiation. The image is displayed in all three planes, i.e. Axial, Coronal, and Sagittal. MRI provides exquisite detail of brain anatomy and generates images with different tissue contrast properties. The magnetic field strength of 0.2 up to 3 teslas is used in clinical settings (52). This study has similarly used 0.35T MRI machines in all of the selected diagnostic centers. This study has applied standard scanning protocols and sequences to perform scans of the brains of pediatric patients. This is similar to the study published in Germany on the benefits of MRI brain imaging in infants which used the same sequences as this study to diagnose not only HCP but also cerebral ischemia, hypoxic-ischemic encephalopathy, and myelination (54). In this study similarly, post-hemorrhagic HCP has been represented in Tables 8 and 11. If imaging examinations were made the standard for the basis of diagnosis and if MRI imaging was made the standard imaging modality to examine infants, as it has no ionizing effect, it would make an enormous change in creating a successful clinical outcome for patients.

6.5. The Risk Factors Associated with Pediatric HCP

6.5.1. Prenatal care given to mothers and HCP

This prospective study identified that 82.4% of the interviewed mothers attended their antenatal visits. Statistical significance was not reached (P> 0.05) among those mothers that did not attend their visits (17.6%). This study hypothesized that those mothers that said they went to their visits may not have attended all the visits they were supposed to go to. This may be explained by poor antenatal follow-ups and this could have resulted in NTDs, which in turn lead to HCP. This study is supported by a study conducted in Atlanta that has suggested that getting adequate prenatal care might help prevent birth defects, HCP being one of them. The study from Atlanta has also suggested the use of peri-conceptional multivitamins are associated with a reduced risk of NTDs (55).

In this study, no association was found with the onset of prenatal care given to the mother and HCP development (P>0.05). This finding is supported by the study from Mississippi that similarly studied potential risk factors of congenital HCP, which similarly did not find any association among prenatal care given to mothers and HCP occurrence (9). This study could not establish a significant association between poor prenatal care given to mothers during their early pregnancy period with that of HCP development. A similar study conducted in Tanzania provides a good insight and has suggested that poor prenatal care given to mothers might contribute to the high incidence of neonatal sepsis, which was included in the post-infectious group reported as an etiologic agent of HCP (51).

6.5.2. Folic acid Supplementation and HCP

Folate deficiency has a recognized teratogenic effect, resulting in an increased risk of NTDs (47). This study argues that the incidence of these NTDs that eventually lead to HCP and other CNS anomalies could have resulted due to the inadequate consumption of folic acid. In this study, mothers who did not take folic acid nutritional supplements were significantly associated with HCP occurrence (P<0.05) (Table 4). During early development, folic acid helps form the neural tube hence, it plays an important role in the prevention of some major birth defects of an infant's brain i.e. (Anencephaly) and spine (Spinal Bifida) (56).

Although the majority (67.8%) of the interviewed mothers in this study did take their folic acid supplement, it was discovered that they took their supplements once they had found out they had conceived and within their late first trimester period and about 32.2 % of these mothers did not take their supplements at all.

This study also found that mothers who took their supplements after they had conceived (58.6%) were significantly associated with HCP development (P<0.05). This study has gathered from this that these mothers did not plan their pregnancy and early consumption of folic acid was not considered. The fact that these mothers did not take their supplements before pregnancy and during their early pregnancy periods could explain the 35.91% and 43.48% of NTDs identified during the retrospective and prospective study period respectively. This study is also in agreement with the study from the Enugu region of Nigeria that similarly suggested that the high incidence of NTDs among the study cohort attributed to the lack of use of folic acid by the majority of the mothers studied, 57 (79.2%) of the affected children (47). This study is also similar to another study that

suggested the consumption of adequate amounts of folic acid by women before pregnancy and during early pregnancy decreases their risk for having a pregnancy affected by NTDs (57).

This study again goes following the study conducted in Northern China that found the supplementation of folic acid reduced the incidence of their study population of total and isolated cases of congenital HCP and NTDs. The study from China also found that the prevalence of HCP declined over the entire study period when a nationwide folic acid supplementation program was introduced (15). Similarly, folate imbalance, deficiency of folate, and vitamin B12 were identified as risk factors for HCP by multiple studies (58-60).

This study supports the findings above. Nevertheless, multivariate analysis of this study was not able to show the inadequate consumption of folic acid as the predictor of HCP occurrence. This has been attributed to the small sample size in the studied population. However, bivariate analysis of this study has found that mothers who did not take the folic acid nutritional supplement were significantly associated with HCP occurrence. As Ethiopia is one of the largest producers of Wheat in Sub-Saharan Africa, (61) and most Ethiopian's diet commonly use Wheat in bread, fortification of wheat flour is an effective, and simple strategy for supplying folic acid and iron to its population (62) thereby reducing the incidence of NTDs that have the potential to lead to HCP.

6.5.3. Advanced maternal age and HCP

Although an association was expected between advanced maternal age and occurrence of HCP, this study did not find a significant relationship between the two ($P>0.05$). It was difficult to find association as the number of interviewed mothers aged above 35 accounted for only 12.4% and these mother's risk of having a child with HCP was not found to have increased; whereby only 8.6% of these mothers had an infant with HCP. This is in agreement with the study conducted in Mississippi that similarly did not find any association with advanced maternal age and HCP occurrence ($P=0.976$) (9).

This study has however found that the majority of mothers (46.4%) were aged 24-29; of these mothers (60.8%) were found to have a child with HCP. This finding among the young mother's age group goes following the study from Atlanta which has also identified HCP without NTDs among young mothers and has reported 1.56 times increased risk among this sect of the population. It was suggested that the most likely explanation for the increased risk for birth defects observed

in these young mothers may be due to different lifestyle factors like inadequate prenatal care, lower intake of vitamins, lowest awareness of folic acid, unhealthy diet, exposure to alcohol, smoking and/or drugs (55).

Young maternal age and advanced maternal age are both associated with increased risks for some types of non-chromosomal birth defects and mothers under 20 and over 35 have a higher risk of giving birth to an infant with a birth defect (55). However, this study was not designed to determine the mechanism by which birth defects occur among different age groups of mothers but further investigation is needed to understand the effects of maternal age on HCP and other birth defects.

6.5.4. Familial Association and HCP

This study was able to show an association between the history of HCP among family members and the development of congenital HCP with a statistical significance of ($P<0.05$) (Table 4); when performing the bivariate analysis. However, the multivariate analysis was not able to show this as a predictor of HCP development and this as mentioned before has been attributed to the small number of study participants. History of HCP among family members was found to account for 73.9% of all the diagnosed cases of HCP. This is similar to a study conducted in Mississippi which reported 72 of 596 congenital HCP cases (12.1%) had at least one additional family member with HCP (9). Although in this study significant association among different degrees of relatives and the development of HCP was not found, it was identified that of the children with HCP, 8.69% had a first degree relative with congenital HCP and these accounted for the majority of HCP diagnosed patients. This result is in agreement with a study conducted in Denmark that also found a significant association of HCP among individuals with first- or second relatives with congenital HCP. The Denmark study suggested that familial aggregation and both the genetic and the maternal effects play important roles in congenital HCP pathogenesis (63). A manuscript published by the American Journal of Medical genetics studied fourteen families in which more than one child was diagnosed with HCP of prenatal onset in their genetic counseling clinic. From the fourteen families, seven were composed of Jewish and Arab families. Of the five of the Jewish family, two were diagnosed with X-linked HCP and three X-linked HCP was suspected (64). This study was unable to adequately analyze genetic sequences due to the lack of genetic laboratories and clinics. Though this study did not investigate genetic agents as a risk factor for HCP, it does recognize its significance and recommends further exploration into the topic for future researches.

6.5.5. Sex preference of HCP

This study did not find any significant association between sex and the occurrence of HCP. X-lined HCP has been reported by the National organization of rare diseases (NORD) as one etiology of HCP (39), and again by the International Society for Pediatric Neurosurgery (ISPN) suggesting that it comprises less than 4% of all cases of HCP (38). This study is in line with the reports of NORD and ISPN that suggest most types of HCP that occur, except for those caused by an X-linked genetic trait, seem to affect males and females equally. Thereby suggesting that there is no obvious sex predilection in pediatric HCP (38, 39). However, as stated earlier, this study did not assess X-linked HCP due to the limited resources (finance and specialized human resource - genetic counselor), and a further detailed investigation was not considered at a genetics level at this time.

6.5.6. Maternal parity and multiple pregnancy and HCP

During the conduction of this study, maternal parity and multiple pregnancies were not identified to be significantly associated with HCP development. This study was contrary to the article published by the University of Ottawa, in Canada, which identified maternal parity and multiple pregnancies as biological risk factors significantly associated with HCP (65).

The result of this study is also contrary to a study conducted in Florida that showed a 46% increased risk of birth defects among multiple births compared to singletons; HCP was identified as one of those birth defects (66), another study in Denmark that investigated familial aggregation of HCP had a higher risk ratio among siblings of multiple births (63), and birth defects among twins studied in Minneapolis, Minnesota, that similarly reported that twins have a greater than a four-fold increased risk of HCP compared to singletons (67). This study however was unable to show the association as the nature of some questions regarding abortion and stillbirth were sensitive and limited information was acquired from mothers during the interview process.

6.5.7. Trauma during Pregnancy

In this study, trauma to the mother during the pregnancy period was not significantly associated with pediatric HCP ($P > 0.05$). This study indicated that 17.3% of mothers of children with HCP suffered from a trauma during their gestation. However, this did not show statistical significance. This is in agreement with a similar study conducted in Mississippi that identified trauma to the

mother during her gestation (3%) and traumatic birth (19.5%) as risk factors for the development of HCP; this study from Mississippi nevertheless did not find this to be statistically significant (9).

In this prospective study, vaginal delivery (78%) and caesarian section delivery (20.9%) accounted for the total number of modes of deliveries questioned. Instrumental delivery was considered a traumatic birth that could have the potential to cause brain injury leading to HCP. Falling accidents during the gestational period were also considered to be causes of fetal brain damage. This goes following a study in Washington State, USA, that reported brain injury as one of the severe birth traumas observed among hospital singleton live births (68).

However, this study was not able to acquire sufficient information from mothers about the details of delivery and only a few of the mothers interviewed were able to recall falling during their pregnancy time. This made it difficult to assess the association; thus making it hard to conclude that birth traumas and accidents were exactly the causes that lead to HCP development. Nonetheless, it hypothesizes that post-hemorrhagic complications that resulted from these traumas could have the potential to lead to HCP.

Even though the etiologies of acquired infant HCP associated with post-hemorrhagic HCP of prematurity were reported to be the most common cause of HCP in more economically developed countries (3), this study has described earlier the contribution of post-hemorrhagic HCP i.e. hypoxic-ischemic cerebral injury, perinatal ischemic insult, subdural hematoma, IVH and cystic encephalomalacia here in Addis Ababa, Ethiopia, a low-income country. Following the initial hypothesis, this study has attributed the occurrence of these post-hemorrhagic complications of acquired HCP to post-traumatic reasons.

6.5.8. The Educational Level of the Mother

Most of the uneducated adults live in South Asia, West Asia, and sub-Saharan Africa, and of all the uneducated adults in the world two-thirds are female. Ethiopia has been grouped as one of the nations with a low literacy rate of 49.1% along with Liberia (literacy rate of 47.6%), Chad (literacy rate of 40.2%), and Mali (literacy rate of 38.7%) (69). By the year 2017 the literacy rate of male and female adults in Ethiopia, was 59.24% and 44.2% respectively which puts Ethiopia's literacy rate the lowest in the world (70, 71). It was presumed in this study that the low level of literacy Ethiopia faces especially in its female population particularly among rural communities would be

one factor for the limited knowledge of these mothers regarding the health of their child. Going in line with this presumption, we found 49.5% of the interviewed mothers to be from the rural population, and 81.3% to be housewives. The findings of this study could be attributed to sociocultural factors, for example, gender violence, early marriage, and the burden of housework that affect women's and girls to not pursue and complete their education. Of the mothers from the rural side, 16.16% of them had a child diagnosed with HCP. In this study, 87.9% of the mothers interviewed did not have any awareness about HCP and had never even heard about it. This study is in line with the article published by Indiana University that reported low health literacy negatively affects a woman's health knowledge, ability to navigate the health care system, and ability to care for her children (72).

Despite not being able to establish a statistically significant association between the mother's educational level and HCP occurrence, different works of literature this study has reviewed has explained its assumptions about the fact that mother's education is important not only to empower these women but to have a better awareness about their child's health. In this study, mothers with an educational level of diploma and above had a reduced rate of children with HCP, about 3.29% were identified. This study is in line with another study conducted where parental occupation was examined as a risk factor for HCP. This study found that engineers' and architects' infants had a reduced risk as compared to janitors who showed a higher risk of HCP among their infants (73).

6.5.9. Maternal Pathologies, Infections, Smoking, Illicit drug use, and Maternal Medication

Maternal chronic hypertension, pre-eclampsia, and maternal diabetes (pre-gestational and gestational) were investigated as risk factors of HCP development, these associations had no statistical significance. This goes in line with reports from the study that similarly did not find statistical significance between maternal diabetes and preeclampsia with HCP development (74). Reports of the prevalence of diabetes and preeclampsia are limited in the developing country setting as opposed to the Western world. For example, a study from Mississippi has identified maternal hypertension during pregnancy to be significantly associated with HCP (9). Unlike this, a study conducted within the eastern zone of Tigray, in Ethiopia has reported the prevalence rate of gestational diabetes mellitus to be only 3.7% (75).

In this study, intrauterine infections, for example, TORCH infections were identified among 9.9% of the mothers. These infections were diagnosed while CT and MRI imaging of the child's brain was performed and HCP was diagnosed. This is in agreement with the study conducted in the University of Athens which also reported an association between maternal infections of toxoplasmosis and cytomegalovirus with congenital HCP but were not able to establish a statistical significance (74). This study found it difficult to reach a statistical significance as the mothers were neither able to explain the type of infection they were diagnosed with nor were they able to know whether they had an infection in the first place. This study has attributed this to the fact that the majority of these mothers were not educated, as previously reported, only 19.8% of the interviewed mothers had a diploma and above. Besides, as some of the viral infections stayed dormant with no clinical signs, this study did not find it surprising these mothers were unaware of the infections. In this study, sexually transmitted infections during pregnancy were identified among 4.4% of mothers. These identified infections were not confirmed by laboratory investigations in this study rather they were gathered from mothers during the interview process. Though this did not reach statistical significance, it goes following the study from Mississippi that similarly reported sexually transmitted infections at the time of delivery were 1.2% but this was not statistically significant (9).

Cigarette smoking and drug use by mothers during their pregnancy were studied as potential risk factors, but statistical significance was not reached. This follows the study from Mississippi which while it reported illicit drug use (3.9%) as a risk factor of HCP, statistical significance was not established. Tobacco smoking during pregnancy was not found to be significant among mothers of infants with HCP either (9). Studies have reported that maternal medication use of antidepressants during the first-trimester pregnancy were found to have a significant association with the development of HCP (74). This study was different from this as interviewed mothers that took prescribed medication in this study however were only 10% and the majority of the mothers were not aware as to what the medications were. As the majority of the mothers interviewed were not educated, this study found it difficult to acquire sufficient information about the exact time and type of medications taken during the pregnancy, and types of treatments they may have received before or during the pregnancy. Statistical significance was not found among maternal use of medications and HCP in this study.

7. STRENGTH OF THE STUDY

•Cross-sectional facility-based study design employed across the four selected diagnostic centers allowed this study to be representative of the study population

8. LIMITATIONS OF THE STUDY

•The limited amount of time and resource the prospective study had has affected the data distribution. Marked reduction in the number of patients during this study period resulted due to the failure of the MRI machine to work during the data collection period. As physicians preferred MRI to diagnose HCP and the unavailability of the machine, as a result, has decreased the total studied population.

• The selected diagnostic centers did not keep the patient's records in a computerized manner and the patient's history was not fully documented in the form of a medical chart as in public hospitals. This made it difficult to acquire all the relevant information about the patient's clinical history and this has affected the retrospective data collection.

9. CONCLUSIONS

Pediatric hydrocephalus presents a colossal challenge in Africa, especially in Sub-Saharan Africa. Ethiopia, a low-income- country faces this problem too. Based on the findings and discussions above, below are major conclusions.

1. High prevalence observed in the pediatric population of both study periods i.e. the retrospective study was 22% and the prospective study was 23%.

2. Aqueductal stenosis was found to be the most prevalent type of congenital HCP, followed by NTDs.

3. Hydrocephalus that developed secondary to infection was minimal whereby 10.1% and 8.69% were observed in the retrospective and prospective study periods respectively.

4. Male predominance was observed in the majority of the retrospective study's pediatric population while females were predominant in the prospective study. Furthermore, this study has observed non-communicating HCP predominance in both study periods and has attributed it to Aqueductal stenosis.

5. Advanced maternal age, maternal parity, multiple pregnancies, maternal pathologies, and sex preference of HCP; the educational level of the mother, attendance of antenatal clinic, and trauma during pregnancy were all studied as potential risk factors for HCP development but statistical significance was not found. Inadequate consumption of folic acid during pregnancy, the onset at which the mothers took their supplement, and history of HCP within the family were significantly associated with the development of HCP but this study was not able to show these as major predictors of the outcome variable. However, infants aged younger than 24months were identified as risk factors (major predictor) that were significantly associated with the development of HCP.

6. Although the educational level of the mother was not significantly associated with HCP occurrence, mothers with an educational level of diploma and above had a reduced rate of children with HCP.

7. The majority of HCP diagnosed patients had first degree relatives with congenital HCP.

8. There is a high association between the amount of folic acid consumption in early pregnancy and the incidence of NTDs. Sufficient utilization reduces the incidence of having a child with NTDs.

9. In this study, hypoxic-ischemic cerebral injury, perinatal ischemic insult, and IVH were all associated with post-hemorrhagic complications of acquired HCP and resulted due to post-traumatic reasons.

10. RECOMMENDATIONS

•It would be ideal if public teaching hospitals affiliated with universities, public and private medical schools, and diagnostic centers across the country conducted similar research regarding the prevalence and risk factors of HCP. This would help in formulating a guideline that can be used across the nation and better understand its public health impact.

•The role of familial association and sex preference of HCP need further investigation. Development of a genetic clinic to assess X-linked HCP detailed gene sequences have the potential to identify HCP cases and tackle this pathology head-on.

• Proper education about the severity of HCP, adequate education to increase women's health literacy, and adequate prenatal care to women must be given especially in rural areas

•Further investigation is recommended to understand maternal risk factors associated with the occurrence of congenital and acquired HCP.

• If a centrally managed database of patient's clinical history among public and private health institutes was organized under the Ministry of Health, it would help keep records for better management of the patient and will also serve as a medical and public health policy input.

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12. ANNEXES

Annex 1- Consent Form (English Version)

Addis Ababa University College of Health Sciences

Department of Anatomy

A questionnaire prepared to assess the prevalence and associated risk factors of Hydrocephalus (HCP)

Written Consent Form

Dear study participant, Good morning/afternoon, my name is Blein Mulugeta, and I am a graduate student at the University of Addis Ababa. I have been working on developing this questionnaire to assess the prevalence and associated risk factors of Hydrocephalus (HCP). For this study, your permission is important to research your child and it will help policymakers to design strategies to give focus on the quality of treatment and management of HCP in the Ethiopian setting. There are no harms associated with this study. You will benefit from this study in sharing and reflecting on your views, concerns, and experiences as a parent or caregiver of a child with HCP.

This questionnaire will ask you about your experience while you were pregnant. There will be sections of questions that will ask you to answer if you've had proper prenatal and postnatal follow up care and if your child has received a proper diagnosis for Hydrocephalus, as well as if you have taken your child to be scanned by different machines once diagnosed with Hydrocephalus. Completing this questionnaire will approximately take 15 to 20 minutes.

Your name will not be written in this form and will never be used in connection with your child's imaging results. All findings from this data will be kept strictly confidential. You are not obligated to permit without your interest. Your decline/refusal to participate will not affect any of the services you should obtain from the diagnostic center. If you feel discomfort to give permission, please feel free to drop out at any time you want.

Thank you, in advance, for your valuable cooperation. If you have any questions/concern you can contact me on the following addresses;-

Principal investigator address: 0910902966

Could I have your permission to continue?

1. Yes, signature_____ 2. No, skip to the next subject.

Informed consent certified by investigator

Name _____Signature_____

Date of permission given _____ Time_____

Consent Form (Amharich Version)

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የአናቶሚ መምሪያ

የሃይድሮሴፋለስ (ኤች.ሲ.ፒ) ስርጭት እና ተያያዥ ተጋላጭነት ሁኔታዎችን ለመመርመር የተዘጋጀ መጠይቅ

የጽሑፍ ስምምነት ቅጽ

ውድ የጥናት ተሳታፊ ፣ እንደምን አደሩ / እንደምን ዋሉ ፣ ብሌን ሙሉጌታ እባላለሁ ፣ እና እኔ በአዲስ አበባ ዩኒቨርሲቲ የምረቃ ተማሪ ነኝ ። የሃይድሮሴፋለስ (ኤች.ሲ.ፒ) ስርጭት እና ተዛማጅ ተጋላጭነት ሁኔታዎችን ለመገምገም ይህንን መጠይቅ በማዘጋጀት ላይ እሠራ ነበር ። ለዚህ ጥናት የእርስዎ ፈቃድ ልጅዎን ለማጥናት አስፈላጊ ነው እናም ፖሊሲ አውጪዎች በኢትዮጵያ ሁኔታ ውስጥ በኤች.ፒ.ፒ ሕክምና እና አያያዝ ጥራት ላይ እንዲያተኩሩ ስልቶችን ለመንደፍ ይረዳቸዋል ። ከዚህ ጥናት ጋር የተያያዙ ጉዳቶች የሉም ። በኤች.ሲ.ፒ. እንደ ህፃን ልጅ ወላጅ ወይም ተንከባካቢ በመሆን ያለዎትን አመለካከት ፣ ጭንቀት ፣ እና ልምዶች በማካፈል እና በማንፀባረቅ ከዚህ ጥናት ተጠቃሚ ይሆናሉ ።

ይህ መጠይቅ እርጉዝ በነበሩበት ጊዜ ስላጋጠሙዎት ነገሮች ይጠይቃል ። ትክክለኛ የቅድመ ወሊድ እና የድህረ ወሊድ ክትትል እንክብካቤ ካለዎት እና ልጅዎ ለሃይድሮፊፋለስ ትክክለኛ ምርመራ ካገኘ እንዲሁም ልጅዎን በልዩ ሁኔታ ለመቃኘት የወሰዱት ከሆነ ፣ልጅዎን በሃይድሮፊፋለስ ከተያዙ በኋላ በተለያዩ ማሽኖች እንዲቃኝ ከወሰዱ እንዲመልሱልዎ የሚጠይቁ የጥያቄዎች ክፍሎች ይኖራሉ ። ይህንን መጠይቅ ማጠናቀቅ በግምት ከ 15 እስከ 20 ደቂቃዎችን ይወስዳል ።

የእርስዎ ስም በዚህ ቅጽ አይጻፍም እና ከልጅዎ የምስል ውጤቶች ጋር በተያያዘ በጭራሽ ጥቅም ላይ አይውልም። ከዚህ መረጃ ሁሉም ግኝቶች በጥብቅ በሚስጥር ይቀመጣሉ። ያለ እርስዎ ፍላጎት የመፍቀድ ግዴታ የለብዎትም። ላለመቀበል / ላለመቀበል ከምርመራ ማዕከሉ ማግኘት ያለብዎትን ማንኛውንም አገልግሎት አይነካም ። ፈቃድ ለመስጠት ምቾት የሚሰማዎት ከሆነ እባክዎ በፈለጉት ሰዓት ለመተው ነፃነት ይሰማዎት ።

ስለ ውድ ትብብርዎ በቅድሚያ አመሰግናለሁ። ማንኛውም ጥያቄ / ጭንቀት ካለዎት በሚከተሉት አድራሻዎች ሊያገኙኝ ይችላሉ ፤ -

ዋና መርማሪ አድራሻ 0910902966

ለመቀጠል የእርስዎ ፈቃድ ማግኘት እችል ይሆን?

1. አዎ ፣ ፊርማ _____ 2. አይ ፣ ወደ ቀጣዩ ርዕሰ ጉዳይ ይዝለሉ።

በመረጃ የተረጋገጠ ፈቃድ በመርማሪው የተረጋገጠ

ስም _____ ፊርማ _____

የተፈቀደበት ቀን _____ ሰዓት_____

Annex 2- Questionnaire

No.	Question	Answer
Section 1: Basic Details of Young Infant		
101	Age of infant	_____
102	Sex of infant	1. Male 2. Female
103	Gestational age at delivery in weeks	_____Weeks
104	Birth weight of infant	_____Kg
Section 2: Maternal Details		
201	Residential area	1. Urban 2. Rural
202	Age of the mother in years	_____years
203	Educational level of mother	1 Did not attend school 2 Elementary school(1-8) 3 High school(9-12) 4 Diploma and above
204	Occupational status of mother	1. Employed 2. Housewife
205	Family average monthly income	1.Governmental 2. Non-governmental 3. Private
206	How many children have you given birth to	_____
Section 3: Risk Factors and clinical characteristics		
301	Did you attend antenatal clinic during the pregnancy?	1. Yes 2. No
302	Did you have abortion in past pregnancy/pregnancies?	1. Yes 2. No
303	Is there history of still birth in past pregnancy/pregnancies?	1. Yes 2. No
304	Mode of delivery of this child	1. Caesarean 2. Vaginal
305	Was your labor prolonged?	1. Yes 2. No
Did you experience any of these complications in pregnancy?		
306	Vaginal bleeding	1. Yes 2. No
307	Trauma	1. Yes 2. No
308	Pregnancy induced hypertension (Pre-eclampsia)	1. Yes 2. No
309	Maternal chronic hypertension	1. Yes 2. No
310	Sexually transmitted disease	1. Yes 2. No
311	Did you receive any treatments for any of the above?	1. Yes 2. No
	If yes, what treatments and for which?	_____

	If yes, at which trimester?	1. First 2. Second 3.Third
312	Did you use folic acid (nutritional supplements) during the pregnancy?	1. Yes 2. No
	If yes, when did you start using them?	1. Before pregnancy(specify) _____ 2. After conceiving (specify) _____
313	Did you take alcohol during pregnancy?	1. Yes 2. No
314	Did you smoke cigarette during pregnancy?	1. Yes 2. No
315	Did you take prescribed medication during pregnancy?	1. Yes 2. No
	If yes, what type of medicaton have you taken	_____
	If yes, was this medication prescribed knowing you were pregnant?	1. Yes 2. No
	If yes, at what gestation age?	_____
316	Do you have Diabetes Mellitus?	1. Yes 2. No
	If Yes, do you use medication regularly	1. Yes 2. No
317	Were you exposed to x-ray irradiation during pregnancy?	1. Yes 2. No
	If yes, how many X ray exposures did you have?	1. 2 or less 2. more than 2
	If yes, at what gestation age?	_____
318	During your pregnancy, were you diagnosed with infection related to the uterus?	1. Yes 2. No
319	Have you ever heard of hydrocephalus (HCP)?	1. Yes 2. No
320	Is there a history of hydrocephalus (HCP) in your family?	1. Yes 2. No
	If Yes, how is that person related to this child?	1. .First degree relative 2. Second degree relative 3. Third degree relative
321	Have you undergone any of these scans during your pregnancy?	1. X-ray 2. CT scan 3. MRI scan 4. Ultrasound
322	Once you gave birth, has your baby been scanned by which one of these?	1. X-ray 2. CT scan 3. MRI scan 4. Ultrasound

Section 4: Radiology Results of Brain CT/MRI Examinations		
401	Clinical indication	_____
402	Type of modality used	1. MRI 2. CT
403	Hydrocephalus confirmed by radiologist report	1. Yes 2. No
404	Type of Hydrocephlaus confirmed by report of radiologist	1.Communicaitng 2. Non communicaitng

THANK YOU VERY MUCH!

Name of Diagnostic Center: _____

Name of data collector: _____

Date of Interview: _____

Signature of Interviewer: _____