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**Myelomeningocele and Hydrocephalus in Uganda: The Intersection of
Culture, Supportive Care, and Long-Term Survival**

**A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine**

by

Ernest John Wright III

2011

Abstract

Myelomeningocele and Hydrocephalus in Uganda: The Intersection of Culture, Supportive Care, and Long-Term Survival. Ernest J Wright III (Sponsored by Dr. Dennis Spencer). Department of Neurosurgery, Yale School of Medicine, New Haven, CT.

The treatment of neurosurgical disease in the developing world presents challenges on numerous levels, not the least of which are the litany of logistical and infrastructural barriers which stand in the way of delivering care. The scarcity of neurosurgeons combined with limited mobility in developing countries requires a reconsideration of approaches to treatment; this is particularly true of ventriculoperitoneal (VP) shunt insertion for the treatment of hydrocephalus. While VP shunt implantation is the mainstay of treatment in the United States, it is prone to failure requiring rapid access to neurosurgical care making shunt dependency a dangerous proposition in this setting. Endoscopic third ventriculostomy (ETV) offers an alternative to VP shunt dependency and has been shown to be effective in treating hydrocephalus at intervals of up to 14 months.

The purpose of this study is to compare the five-year survival for children treated with endoscopic third ventriculostomy (ETV) to those treated with ventriculoperitoneal (VP) shunt implantation for myelomeningocele-associated hydrocephalus. Because of the well known dangers of shunt dependency, it is hypothesized that patients treated with ETV will have a survival advantage when compared with patients treated with VPS at a follow-up interval of five years.

In order to address this hypothesis, a retrospective observational study of children treated with ETV or VP shunt implantation for myelomeningocele-related hydrocephalus at the CURE Children's Hospital of Uganda was carried out, including a control group consisting of myelomeningocele patients who had not developed hydrocephalus.

Survival status was determined for 128 of 131 study participants (98%). 47/128 (37%) of patients had expired at five years post-treatment, and 55/128 (42%) patients had expired at a mean follow-up interval of 84.4 months. Only two cases of death were attributable to the development of hydrocephalus, none as a result of treatment failure. Kaplan-Meier survival analysis found no statistically significant relationship between survival and method of treatment for hydrocephalus ($p=0.45$), sex of patient ($p=0.53$), HIV status ($p=0.69$), age at repair ($p=0.34$), or myelomeningocele level ($p=0.12$). Survival analysis performed for districts with community based rehabilitation (CBR) programs and districts without CBR programs revealed a significant interaction ($p=0.001$).

The uniformly high mortality across all groups suggests that the chief causes of long-term mortality are both powerful and independent of hydrocephalus. The only correlation with survival identified in this study, the presence of a CBR program providing in-home rehabilitation, fulfills both of these criteria: myelomeningocele patients require long-term rehabilitation regardless of the development of hydrocephalus and these programs exert a powerful influence on survival. This substantial difference in long-term survival highlights the fact that children in communities without CBR programs are not receiving life-saving supportive care, in part due to a lack of parental understanding of the need for longitudinal care. Established cultural beliefs about myelomeningocele,

hydrocephalus, and disability in general also hampered efforts to improve survival.

Understanding the practical barriers to the delivery of care in a developing country as well as the cultural mores through which diseases are understood are critical to effectively treating disease across cultures and continents.

Acknowledgements

I would like to thank Drs. Benjamin Warf and Dennis Spencer for their kindness and mentorship over the past years which have culminated in this thesis project. I would also like to thank all of the residents and faculty members in the Department of Neurosurgery at the Yale School of Medicine who have supported and nurtured my interest in neurosurgery, Dr. Abhaya Kulkarni for offering his statistical knowledge and guidance in data analysis, and the Yale Office of Student Research for funding this project.

I would especially like to thank my parents, Ernest and Alica Wright, as well as my sister Nicole Wright for their unconditional love and belief in me. And finally, I owe a great debt to my dear friends: Whitney Tolpinrud, whose love and support buoyed me during my time in Uganda, and Bryan Hong, a true friend and gifted illustrator who gave so generously of his time provide the images for our children's book *Everyone is Different*.

This thesis is not the product of any one person, but rather is a product of the contributions of the people mentioned above. For them and all the ways that they have touched my life, I will always be grateful.

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Introduction

Mbale, Uganda is a frontier town of sorts: situated five hours from the capital Kampala, it is the last major stop on the road to the Northwestern border with Sudan and Kenya. It is an unlikely place to receive neurosurgical care, yet since the year 2000 it has been home to the CURE Children's Hospital of Uganda, the sole treatment center dedicated to pediatric neurosurgery in sub-Saharan Africa. When the Hospital opened, it brought to the region for the first time the possibility of survival for children born with hydrocephalus and myelomeningocele, diseases that are most often fatal when untreated. In two modern neurosurgical operating suites treatment for these diseases is dispensed in the model of the developed world where children receive an initial surgical procedure at the hospital and are discharged home with instructions to return to the Hospital for follow-up care. With such a neurosurgical outpost utilizing proven treatment paradigms, it is expected that the results should be dramatic: where few children had survived these diseases in the past, few should be dying of these ailments in the present. The efficacy of these treatments at intervals beyond 14 months is unknown however, as greater than 70% of these patients have been lost to follow-up five years after their initial treatment. The fate of these patients, whether they are surviving or expired, and ultimately whether treatment has been effective in intervening in the natural course of disease is unknown. What follows is an attempt to answer this question, but also to better understand how to adapt a technically complex and technology-dependent field such as neurosurgery to the setting of a developing country where even the electricity to power the many devices that modern neurosurgeons depend on cannot be taken for granted.

Neurosurgery in the Developing World

There are few areas within medicine that have changed as much in the span of a half-century as neurosurgery. Advancements beginning with the implementation of the operating microscope in 1957 heralded the age of modern neurosurgery, in which dauntingly complex pathology is now treated routinely with greater precision, less morbidity, and lower mortality(1, 2). While the field has made a practice of conscripting cutting-edge technology to advance the frontiers of neurosurgery, the fact remains that the overwhelming majority of the six billion citizens of the world have languished with no neurosurgical care at all. A full 60% of the world's neurosurgeons administer care to just 14% of the global population; the remaining 40%, 9,686 neurosurgeons, are responsible for 4.66 billion individuals(3). In addition to inequities in the distribution of neurosurgical talent, neurosurgically treated illness exerts a disproportionate toll on the citizens of the developing world. Hydrocephalus, a disease of excess cerebrospinal fluid in the ventricular system of the brain, has been shown to have a higher prevalence and affect a larger number of children in East Africa (4). Neural tube defects, debilitating congenital malformations requiring neurosurgical repair of which the most severe variants are termed myelomeningocele, are the most frequently encountered congenital malformation in sub-Saharan Africa(5). Given this disproportionate disease burden and the scarcity of neurosurgical care, attention must be given to the treatment of neurosurgical diseases in the third world to ensure that as the frontiers of neurosurgery are advanced in the first world the remainder of the world's population is not left behind.

The necessary solution to this problem lies not in simply exporting first world treatment paradigms, but in developing treatments tailored to the developing world. The factors which complicate daily life in developing countries- namely shortcomings of government, disparities in purchasing power, and a lack of basic infrastructure- also present unique challenges to the delivery of neurosurgical care. Unstable or inefficient systems of government prevent the administration of an effective public health apparatus, disparities in purchasing power place medical devices and pharmaceuticals beyond reach of the majority of the populace, and a lack of investment in infrastructure presents barriers to both communication and travel. First world treatment paradigms that take these things for granted are doomed to fail in this setting. The challenging realities of life in the developing world necessitate a unique approach to treatment which takes into account the unique limitations of treating disease in a resource-limited setting.

Hydrocephalus in Uganda

The necessity for a considered approach to neurosurgical disease in the developing world is illustrated by examining efforts in Uganda to treat hydrocephalus. Uganda is emblematic of many developing countries in its shortage of trained physicians rendering specialized care: there are only four neurosurgeons serving its population of 30,000,000 citizens(4, 6). Further exacerbating this scarcity is the fact that most healthcare providers are located in urban settings while the majority of the populace is dispersed throughout rural areas: three of the four neurosurgeons are located in the capital city Kampala while 87% of the population lives outside of urbanized population

centers(6, 7). For the relatively few Ugandans with access to a neurosurgeon, treatment remains elusive because of the prohibitive cost of neurosurgical care. The price of the implantable hardware which comprises the mainstay of treatment for hydrocephalus in the US is \$650, more than one and a half times the gross national income per capita of \$420 and an exorbitant sum for the half of the Ugandan population living on less than a dollar a day(7, 8). The dearth of neurosurgeons combined with their geographic sequestration and the lack of affordable treatment options places first world neurosurgical care outside of the reach of the vast majority of the Ugandan population.

Beyond these myriad challenges endemic to developing countries that stand in the way of the delivery of medical care, the nature of disease itself can differ when presenting in the developing world. This point is well illustrated by comparing the causes, presentation, and sequelae associated with hydrocephalus as it presents in the United States and Uganda. While hydrocephalus in the United States is most often congenital in origin(9), hydrocephalus in Uganda is most often secondary to infection(10, 11). In the United States and most developing nations, hydrocephalus is often detected when a child's head circumference departs from normal growth curves during routine health screening. In Uganda where such screening is rare, hydrocephalus presents at a much more advanced stage as gross cranial enlargement with overt signs of increased intracranial pressure such as nausea and vomiting or paralysis of upward gaze(10). Perhaps most importantly in terms of long-term survival, routine complications that are considered benign in developed countries can have far more serious consequences in the setting of a developing country. Hydrocephalus is commonly treated with a

ventriculoperitoneal shunt (VPS) device that connects the ventricular system of the brain to the peritoneal cavity, creating a path of egress for excess intraventricular cerebrospinal fluid. Shunt infection and malfunction are common, manageable complications given rapid access to neurosurgical care; however in a setting where antibiotics are unavailable and neurosurgical care a day's journey or more these complications can be lethal. Given these fundamental differences in etiology, stage at presentation, and complications, it can be said that hydrocephalus in the United States and Uganda share a common pathophysiological basis but little else.

The challenges and barriers to the delivery of healthcare in the developing world are protean. In Uganda, factors both intrinsic and extrinsic to medicine fashion hydrocephalus as a distinct pathological entity in a setting of limited resources and trained personnel. In this setting where simple tasks are complicated and traditionally manageable complications take on lethal consequences, a departure from conventional treatment paradigms is required to safely and successfully treat hydrocephalus.

Alternative Approaches to the Treatment of Hydrocephalus

Ventriculoperitoneal shunt insertion is generally held to be the standard of care for the treatment of hydrocephalus(9). There is no published data on the morbidity and mortality associated with shunt failure in developing nations. However, the extensive body of work enumerating the morbidity and mortality associated with shunt dependency in developed countries suggests that shunts fail at high rates and with regularity throughout the lifetime of the patient. The most comprehensive trial to date on shunt

failure found that over half of ventriculoperitoneal shunts fail within two years of implantation, which is in accord with previously reported failure rates in the literature(12-15). Beyond this high initial failure rate, shunt dependency is an ever-present danger as shunts continue to fail throughout the lifetime of the patient at a rate of 5% per annum(16). While shunt infection and failure are manageable complications given appropriate antibiotics and rapid access to neurosurgical care, in a setting where neurosurgeons and antibiotics are scarce shunt dependency is presumably a dangerous proposition.

Endoscopic third ventriculostomy (ETV) offers an alternative to shunt implantation and shunt dependency for the treatment of hydrocephalus by creating an alternative communication between the ventricular system and the subarachnoid space through fenestration of the floor of the third ventricle. Third ventriculostomy has been employed since the dawn of modern neurosurgery for the treatment of hydrocephalus: the first third ventriculostomy was performed by Dandy in 1922 with the first endoscopic procedure by urologist Walter Mixter in 1923 for which he provided successful treatment of non-communicating hydrocephalus in a nine-month old child(17). In the ensuing decades, ETV was performed under stereotactic or ultrasound guidance with varying degrees of success. The development of silicone and improvements in valve design in the latter half of the 1950's led to ETV being superseded by VP shunt implantation for the treatment of hydrocephalus. In recent years however, advances in neuroendoscopy have led to a resurgence of interest in ETV.

ETV represents an attractive alternative to VP shunting for the treatment of hydrocephalus in the developing world. Avoiding implantation of shunt hardware has

multiple benefits: not only does this obviate the per-procedure cost of a medical implant, but the risk of infection is reduced substantially because no foreign bodies are introduced into the patient. Most importantly, an alternative to shunt implantation allows one to circumvent the dangers of shunt dependency and malfunction that have been well documented in the United States and throughout much of the developed world.

Through a series of studies performed at the CURE Children's Hospital of Uganda (CCHU), Warf et al have sought to define a role for ETV in the treatment of hydrocephalus in the developing world(8, 10, 18, 19). In a prospective study involving 229 patients with hydrocephalus treated by ETV, Warf et al examined the interaction between efficacy of ETV and several categorical variables including age at treatment, cause of hydrocephalus (infectious vs. non-infectious), and patency of the cerebral aqueduct(10). The overall success rate of 59% obscures the fact that the success of ETV varied widely between age groups and hydrocephalus of differing etiology. ETV was highly effective in patients greater than one year of age, with success rates of 81% in cases of non-postinfectious hydrocephalus (NPIHC) and 90% in postinfectious hydrocephalus (PIHC). In patients less than a year of age ETV was markedly less effective: 59% of patients with PIHC and just 40% of patients with NPIHC were successfully treated with ETV. However, in patients less than one year of age those with an obstructed cerebral aqueduct (as assessed by fourth ventricular size on ultrasound) were well suited to treatment by ETV with a success rate of 70%. Based on these findings, Warf contends that ETV can be considered for primary treatment of hydrocephalus patients older than

one year of age irrespective of etiology and in patients younger than one year of age with PIHC and a closed aqueduct.

In a subsequent prospective study involving 550 patients, Warf sought to characterize the potential benefits of combining choroid plexus cauterization (CPC) with ETV for the treatment of hydrocephalus(18). While there was no demonstrated benefit in patients operated on at one year of age or greater, patients less than one year of age received a significant benefit from the addition of CPC with 66% of patients being effectively treated in comparison to 47% for ETV alone. Notably, the follow-up intervals for the two groups differed significantly with a mean follow-up of 9 months for the ETV/CPC group and 19.2 months for the ETV group, leaving open to question the possibility that late failure in the ETV/CPC group may have diminished the claimed benefit of the combined procedure. The benefits of combining ETV with CPC are even more dramatic in several subgroups: the success rate in NPIHC increased from 38% to 70% with the addition of CPC, and from 35% to 76% in cases of myelomeningocele-associated hydrocephalus.

Given the promising results of the combined ETV/CPC procedure in the treatment of myelomeningocele-associated hydrocephalus, Warf et al undertook a subsequent prospective study involving 115 patients with myelomeningocele-associated hydrocephalus treated with ETV/CPC to establish the efficacy of the combined procedure at intervals of one year or greater(19). It was found that ETV/CPC was effective in 76% of patients at mean follow-up of 19 months. Further, when ETV failure occurred the failure presented before 10 months in all patients, and before 6 months

almost 90% of patients. These results suggest that ETV/CPC is an effective treatment for myelomeningocele-associated hydrocephalus and that treatment failure occurs relatively early in the post-operative course, averting the lifelong surveillance required with shunt dependency.

While these studies provide an evidentiary basis for the idea that ETV and combined ETV/CPC in particular offer a genuine alternative to shunt implantation for the treatment of hydrocephalus, the all-important question remains whether ETV/CPC offers an actual survival benefit in comparison to VP shunt implantation for the treatment of hydrocephalus. This is the question that this study seeks to address.

Statement of Purpose: Specific Hypothesis and Aims

The purpose of this study is to determine the five-year survival for children treated with ETV or VP shunt implantation for myelomeningocele-associated hydrocephalus between 2000 and 2005 at the CURE Children's Hospital of Uganda.

Specifically, I hypothesize that either ETV or the combined ETV/CPC procedure is associated with a lower mortality rate than VP shunt implantation for the treatment of myelomeningocele-associated hydrocephalus in Southeastern Uganda at a follow-up interval of five years.

Additional aims of this study include elucidating the long-term outcome for children with myelomeningocele and hydrocephalus in East Africa, which is heretofore unknown.

Methods

Study Site

In order to address this hypothesis, the author undertook a retrospective observational study of children treated with ETV, ETV/CPC, or VPS implantation for hydrocephalus at the CURE Children's Hospital of Uganda (CCHU).

CCHU located in Mbale, Uganda is sub-Saharan Africa's only dedicated pediatric neurosurgical hospital with one attending neurosurgeon performing over 1,000 procedures per year. CCHU represents an ideal site for this study by virtue of its location and existing population of hydrocephalus patients treated with ETV and VPS since the year 2000.

After receiving approval from the institutional review boards of CCHU and Children's Hospital Boston, the author relocated to Mbale for patient selection and data collection under the guidance of Dr. Benjamin Warf and Dr. Dennis Spencer.

Patient Selection

All patients who present to CCHU are entered into a database containing identifying information, demographic data, diagnosis, and a record of all surgical procedures and follow-up visits. A list of prospective participants in this study was generated by searching this database for myelomeningocele patients presenting between the year 2000 and the end of 2004, yielding a follow-up interval of five years or greater. Because of the difficulty involved in tracking patients living at distances of more than one day's travel from CCHU, this list was restricted to patients residing in the sixteen

districts of southeastern Uganda. This list was further restricted to patients who had survived longer than one month after surgery to eliminate early deaths due to surgical complications, patients who had a minimum of six months of follow-up to eliminate those who failed to return for any follow-up appointments, and patients who presented before six months of age to eliminate cases of delayed myelomeningocele closure.

Experimental design

From these criteria participants in the study were identified and divided into three groups: two treatment groups and one control group. Participants were segregated by treatment method into an ETV group including patients who received either an ETV or combined ETV/CPC, and a VP shunt group. The control group consisted of myelomeningocele patients who had not required any treatment for hydrocephalus.

The mode of primary treatment was chosen as a function of date at presentation: patients presenting for the treatment of hydrocephalus between 2000 and October 2001 were treated with VPS, between October 2001 and February 2003 ETV, and from February 2003 onwards the combined ETV/CPC procedure. Patients who failed endoscopic treatment were treated with VP shunt implantation.

Outcome measures and patient tracking

The outcomes for this study are survival status and the development of hydrocephalus. A patient was considered alive if he/she had been seen at the most recent annual follow-up visit or at greater than five years of age. The survival status of patients who had missed their last follow-up visit was unknown. Efforts were made to locate these patients by conducting home visits in the patient's villages. When families were located,

the survival of the patient was ascertained and the family was encouraged to return to the hospital for follow-up care if the patient was alive. Patients who could not be found despite these exhaustive efforts were considered definitively lost to follow-up and labeled as such.

A patient was deemed expired if expiration was noted in their medical record or if the patient's parents had indicated that the patient had expired at a home visit. In cases where patients had expired, efforts were made to determine the date of death and circumstances surrounding the death through an extensive questionnaire (Fig 1) with the ultimate goal of distinguishing deaths due to hydrocephalus from those of other causes.

<p style="text-align: center;">Treatment of Hydrocephalus Long Term Follow-Up Cause of Death Questionnaire</p> <p>Date of interview:</p> <p>Location:</p> <p>Interviewer:</p> <p>Patient information</p> <p style="padding-left: 20px;">Name:</p> <p style="padding-left: 20px;">Date of death:</p> <p style="padding-left: 20px;">Age at death:</p> <p>Cause of death according to family members (family narrative):</p>	<p style="text-align: center;">Symptoms (including when the symptoms started and how long the specific symptoms lasted):</p> <ul style="list-style-type: none"> • Headache <ul style="list-style-type: none"> -Did it get worse as time passed? -Was it worse after sleeping? -Was it worse when coughing, going to bathroom? -Did the child awaken from sleep at night complaining of headache? • Vomiting • Weakness or difficulty moving on one side of the body • Difficulty walking • Neck pain • Changes in seeing or blindness • Eyes looking downward • Different sized pupils • Seizure (shaking all over) • Personality change • Drowsiness or loss of consciousness preceding death • Fever <ul style="list-style-type: none"> -Did the fever occur every day or every other day?
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Figure 1: Cause of Death Questionnaire featuring open-ended questions and checklist of symptoms to elicit circumstances surrounding a patient's death

Determination of hydrocephalus

Those patients noted to have developed hydrocephalus in their hospital charts and those who died with a constellation of symptoms indicative of increased intracranial pressure (nausea and vomiting, headache, progressive lethargy) were considered to have developed hydrocephalus. Patients up to date with follow up appointments but without signs or symptoms associated with hydrocephalus were considered not to have developed hydrocephalus. Patients who were initially lost to follow-up but found alive without receiving any subsequent neurosurgical treatment after myelomeningocele closure were considered not treated for hydrocephalus, as were patients who expired without evidence of increased intracranial pressure and patients definitively lost to follow-up.

Analysis/statistical methods

Kaplan-Meier survival curves were constructed to estimate population survival from this sample. The log-rank test was used to assess the interaction between survival and categorical variables including method of treatment, myelomeningocele lesion level, development of hydrocephalus, gender, and HIV status. The univariate Cox proportional hazards model was used to examine the effect of age at closure on survival. These analyses were performed by Dr. Abhaya Kulkarni.

Results

Study Population and Follow-Up Status

Between the year 2000 and 2005, 224 patients had a myelomeningocele closed at CCHU. 140 patients met the inclusion criteria for this study. 41 patients were known to

have expired per hospital records; nine because of death attributed to peri-operative mortality and resultantly were excluded from this analysis of long-term survival (Table 1)(19). 23 patients were seen in clinic at a follow-up interval of greater than five years and considered surviving for the purposes of this study. Survival status was not known for 76 patients. 71 patients were visited in their home villages. Survival status was determined via telephone for two patients because of relocation to a district outside of the southeastern Uganda. Three patients were ultimately lost to follow-up despite all efforts, with survival status unknown.

Cause of Death	Number of Patients (n = 9)
Aspiration	2
Meningitis	2
Ventriculitis	1
Cardiac Arrest (unknown etiology)	1
Anesthesia Complication	1
Suffocation in Bed	1
Unidentified Illness	1

Table 1: Patient mortality during the perioperative period (within one month of surgery). There were no known failures of treatment for hydrocephalus leading to death in the perioperative period.

Survival Analyses

For the 131 patients included in the analysis, survival status was ascertained for 128 (98%) patients. At five years post-treatment, 81/128 patients were surviving and 47/128 expired, yielding five-year survival and mortality rates of 63% and 37% respectively. At the

time of data collection, 73/128 (56%) patients were alive at a mean follow-up interval of 84.4 months and 55/128 (42%) patients were found to have expired (Figure 2).

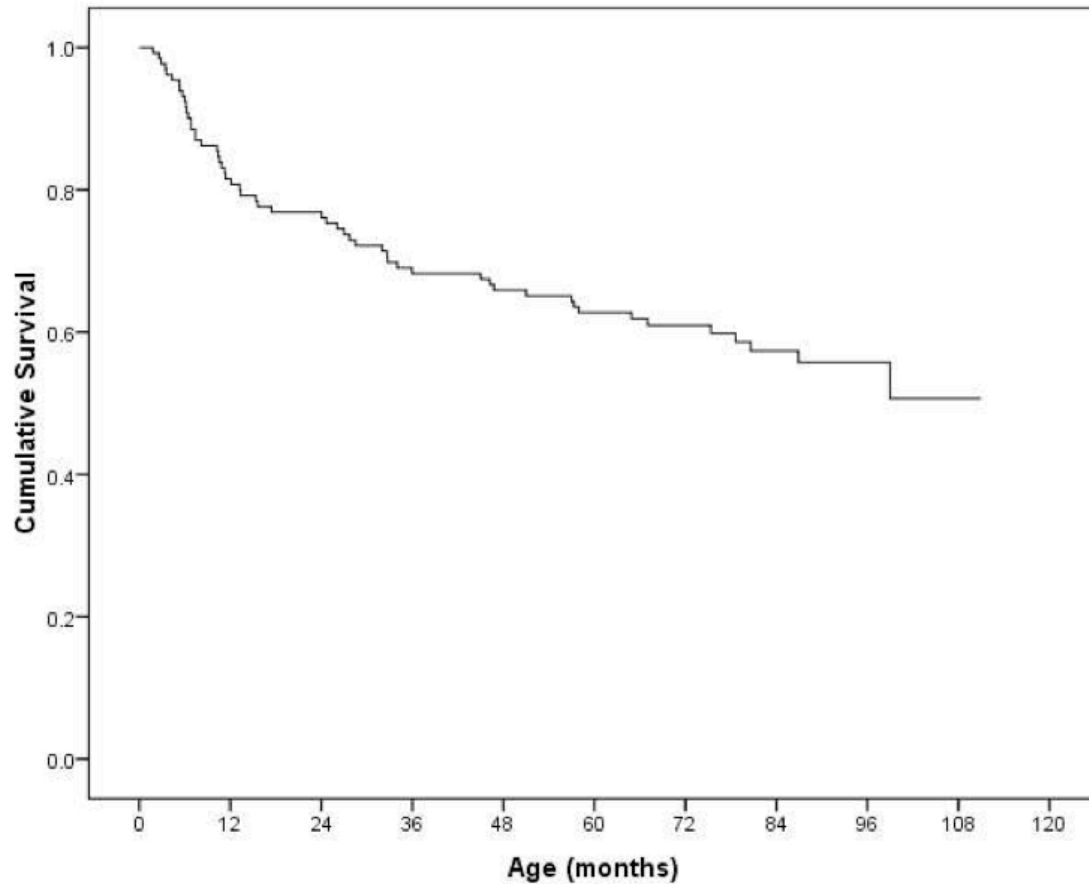


Figure 2: Kaplan-Meier survival curve for all study participants. The initial 12-24 months following treatment represents the greatest threat to survival, although mortality continues steadily throughout the time period measured in this study with 37% of study participants expired at five years after treatment.

Of the 55 patients who expired, a cause of death was ascertained through medical records or by inference based on the symptoms described in the Cause of Death Questionnaire for 35 patients (64% of the instances of death). The causes of death are described in Table 2. Notably, only two cases of death occurred with symptoms suggestive of increased intracranial pressure consistent with the development of

hydrocephalus. These two patients had not been treated for hydrocephalus; as such, neither can be considered treatment failures.

Cause of Death	Number of Patients (n = 55)
Unknown	20
Malaria	11
Unspecified febrile illness	5
Anemia, Malnutrition, Dehydration	4
Gastroenteritis	3
New onset hydrocephalus	2
Parental neglect	2
Pneumonia	2
Measles	1
Pyelonephritis	1
Encephalitis	1
Ventriculitis (post-ETV)	1
Severe burns	1
Chiari	1

Table 2: Causes of death in expired study participants, with only two cases of death attributable to hydrocephalus. Notably, these two patients did not receive treatment for hydrocephalus and as such cannot be considered failures of treatment.

Survival analysis found no statistically significant relationship between survival and method of treatment for hydrocephalus ($p=0.45$, Figure 3a), sex of patient ($p=0.53$), HIV status ($p=0.69$), or age at repair (range 1-126 days of age, mean 20.6 days, median 8 days, $p=0.34$). The interaction between anatomical myelomeningocele level and survival approached but failed to achieve statistical significance ($p=0.12$, Figure 3b).

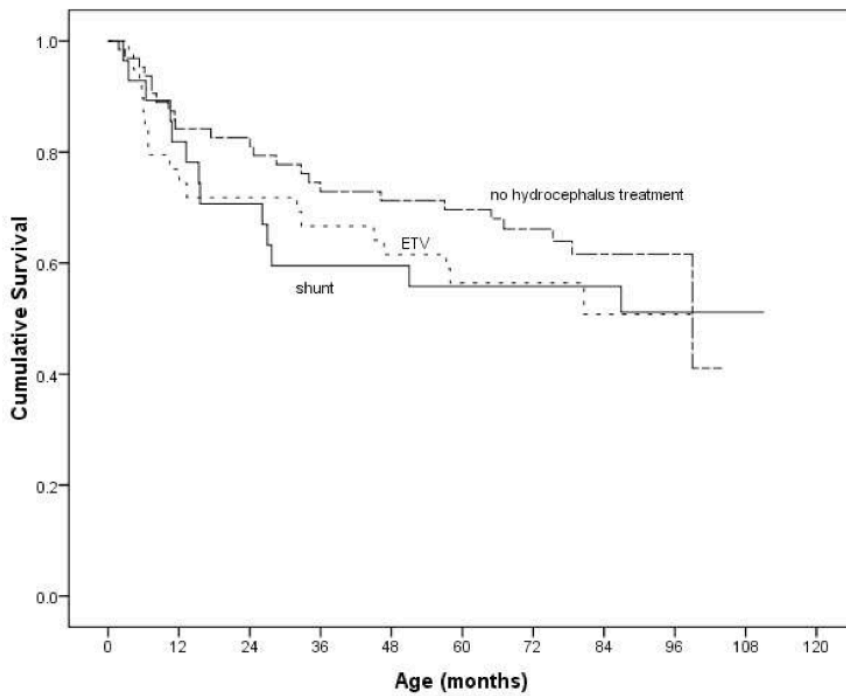


Figure 3a: Kaplan-Meier survival curves for treatment groups and the control group

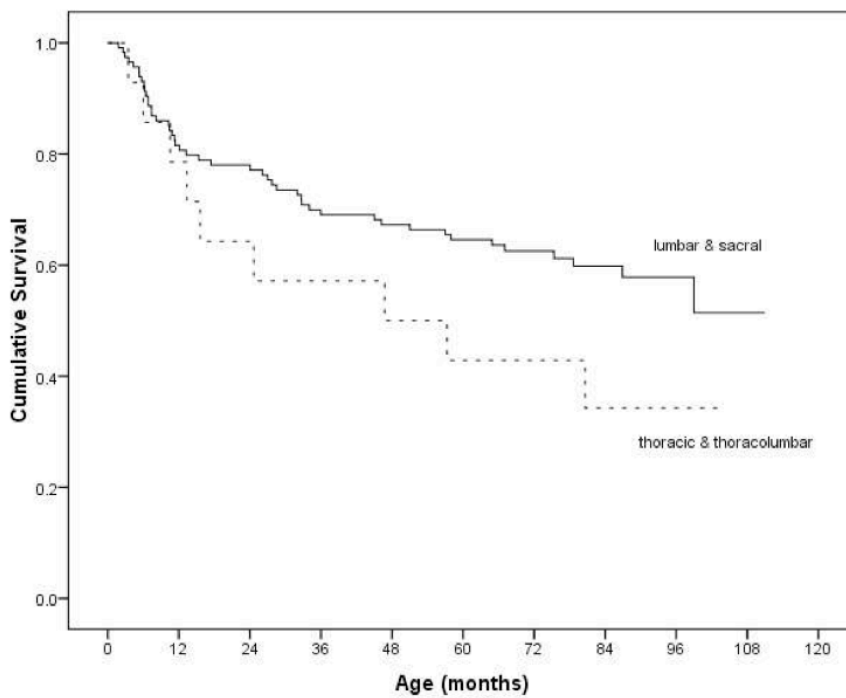


Figure 3b: Kaplan-Meier survival curves for lumbar/sacral and thoracic/thoracolumbar myelomeningocele lesions.

Survival rates varied widely by district, with no discernable geographic trend to explain the variation in mortality (Figure 4). Because a number of districts contributed very few patients to this study, with four districts contributing less than five patients (Table 4), survival analysis by individual district was not attempted. However, survival analysis was performed for districts with community based rehabilitation (CBR) programs (five districts, $n = 48$ patients) and districts without CBR programs (11 districts, $n = 83$ patients). This revealed the only statistically significant interaction in this study, between the presence of a CBR program and five year survival, with a p value of 0.001 (Figure 5).



Figure 4: Mortality rates by district. There is no readily discernable geographic trend which explains the widely varying mortality rates across districts.

District	Total Number of Patients	Number Surviving (%)	Number Expired (%)
Bugiri	3	1 (33%)	2 (66%)
Busia	5	3 (60%)	2 (40%)
Iganga	9	5 (56%)	4 (44%)
Jinja	9	4 (44%)	5 (56%)
Kampala	6	5 (83%)	1 (17%)
Kamuli	7	6 (86%)	1 (14%)
Kapchorwa	4	1 (25%)	3 (75%)
Katakwi	2	0 (0%)	2 (100%)
Kumi	14	10 (71%)	4 (29%)
Mayuge	7	4 (57%)	3 (43%)
Mbale	23	7 (30%)	16 (70%)
Mukono	2	0 (0%)	2 (100%)
Pallisa	8	7 (88%)	1 (12%)
Sironko	9	4 (44%)	5 (56%)
Soroti	7	4 (57%)	3 (43%)
Tororo	16	12 (75%)	4 (25%)

Table 4: Patient number, mortality, and survival by individual district. Mortality (and conversely survival) varied widely across districts. However, the variation in the number of patients contributed by individual districts prohibited survival analysis by individual district.

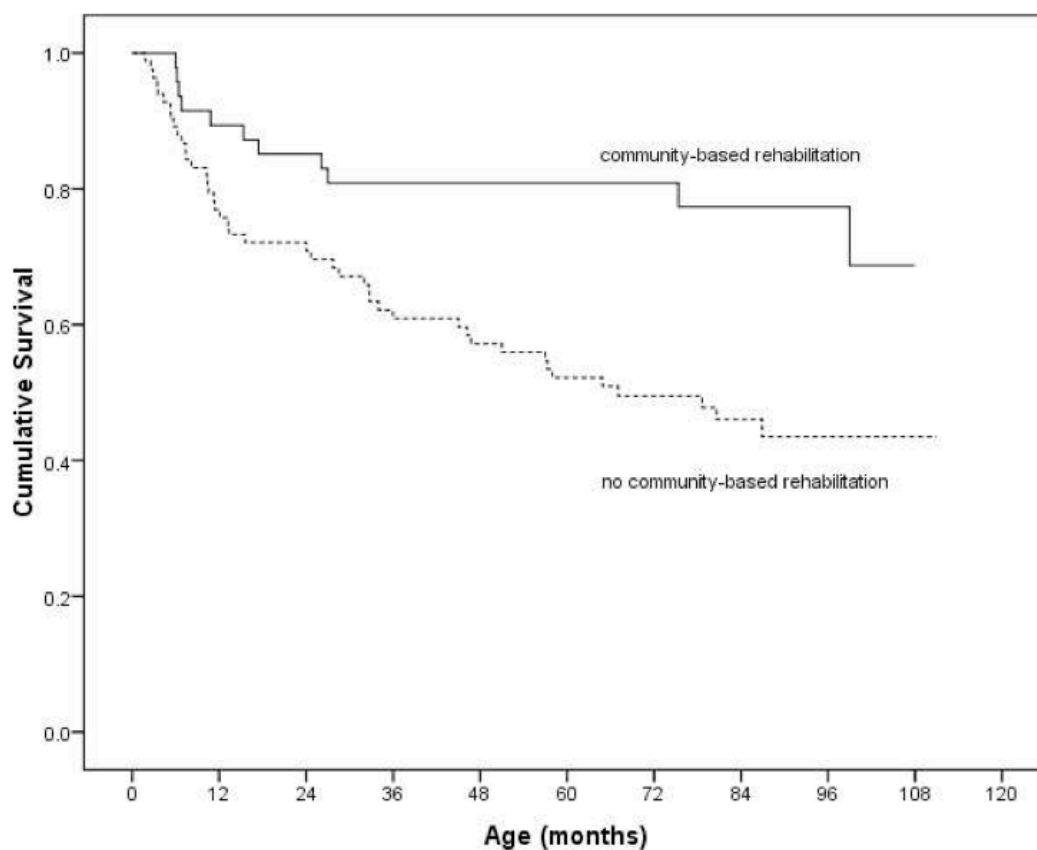


Figure 5: Kaplan-Meier survival curves for districts with and without community based rehabilitation (CBR) programs. Note the dramatic divergence between survival curves and the substantially lower mortality in districts with CBR programs.

Development of hydrocephalus

Of the 131 patients in the study, 67 (51%) had received treatment for hydrocephalus at the time of data collection. 64 (49%) had not required treatment at the time of data collection. Of those requiring treatment for hydrocephalus, 39 patients were primarily treated with endoscopy and 28 primarily treated with shunt implantation. ETV was successful in 9/17 (53%) patients, and combined ETV/CPC was successful in 17/22 (77%) patients. 13 patients failed endoscopic treatment and had ventriculoperitoneal shunts implanted. For the 13 patients who failed endoscopic treatment, all failures occurred

within nine months and 12/13 (92%) occurred within six months of initial endoscopic treatment.

Discussion

Little is known about the fate of patients with myelomeningocele in sub-Saharan Africa. Of the handful of studies reported in the literature, most are descriptive epidemiological studies(20, 21) and the few studies which attempt to describe the course of myelomeningocele suffer from a very small sample size or limited follow-up(22-24). The study reported here involving over 100 patients followed for a minimum of five years with less than 5% of the study population lost to follow-up is the first to offer insight into the challenges and consequences of myelomeningocele in sub-Saharan Africa over the long term.

Determinants of Long-Term Survival

The primary objective of this study is to investigate whether the theorized benefits of ETV and the avoidance of shunt dependency translate into an actual long-term survival benefit for patients with myelomeningocele-related hydrocephalus living in a developing country. Of the 131 patients who met the inclusion criteria for this study, survival status was ascertained and verified for 128 patients (98%) at a mean follow-up interval of 84.4 months, yielding a robust data set. Based on this data, Kaplan-Meier survival analysis revealed no interaction between treatment modality and survival at five years post-treatment ($p=0.45$, Fig 3a). Of interest is the finding that there is no difference in survival between the treatment groups and the control group, which required no treatment for hydrocephalus, suggesting that the factors influencing long-term survival may be

altogether independent of the development or treatment of hydrocephalus. This idea is supported by the results of attempts to elucidate a cause of death for expired patients: hydrocephalus was implicated in only 4/55 (7%) of deaths (Fig 2). The fact that there was no correlation identified between survival and a host of categorical variables (sex, HIV status, age at repair, anatomical myelomeningocele level) suggests that the chief determinants of long-term survival may be powerful enough to obviate the more subtle influence of these categorical variables on survival.

The idea that there are powerful yet unidentified determinants of long-term survival in this population is lent credence by the exceedingly high mortality rate for the participants in this study, which stands at 36% at five years of age. This is significantly higher than 20-25% mortality reported in earlier studies of myelomeningocele in sub-Saharan Africa; this difference is likely attributable to the shorter follow-up intervals of these earlier studies(23). By comparison, the most recent UNICEF figures available for Uganda place the under-5 mortality rate at 18%, making mortality among the participants of this study double that of the general population. With these figures in mind, elucidating the primary determinants of mortality is of great importance in prolonging survival for this population of patients.

Insight into one of the primary determinants of long-term survival can be found through examining an unexpected finding of this study: the large variability in mortality across districts. Despite the uniformly high mortality among all study participants, mortality rates for individual districts ranged from 12-100%. Although this can in part be attributed to the fact that some districts contributed very small numbers of patients and

are thus susceptible to errors of random sampling, mortality rates among the three districts contributing the most patients varied considerably from 25 to 70% suggesting a genuine and substantial variation in mortality rates across districts.

A closer examination of the three districts contributing the largest number of patients to the study (Mbale, Tororo, and Kumi) reveals a potential explanation for this disparity (Fig 4). These three contiguous districts are in close geographical proximity and as such share many demographic characteristics. Despite this fact, they have dramatically different mortality rates: 25% in Tororo, 29% in Kumi, and 70% in Mbale. These results are particularly surprising given that Mbale district, where the CURE Children's Hospital of Uganda is located, has one of the highest mortality rates among the districts included in the study. An extensive search for potential explanatory factors revealed a key dissimilarity between the two districts with dramatically lower mortality rates and Mbale district: the existence of a community based rehabilitation (CBR) program that offers in-home support and training to parents of children with myelomeningocele. Survival analysis of the interaction between the presence of a CBR program and five year survival revealed a dramatic survival advantage in districts with CBR, as is reflected in the Kaplan-Meier survival curve (Fig 5).

The Importance of Accessible Long-Term Care

The importance of long-term supportive care for myelomeningocele patients is well established, with a "life-long commitment by patient, family, and treating medical personnel" required for long-term survival(25). This is certainly no less true in Uganda,

although the provision of such comprehensive, longitudinal care is far more difficult given the lack of a public health infrastructure and the limitations of resources.

Studies in the United States and Europe have demonstrated that long-term mortality in Myelomeningocele is attributable to secondary effects of disease, most commonly renal failure as a consequence of urinary incontinence(26, 27). In acknowledgement of this fact, CCHU has programs in place to provide the materials and instruction to treat urine and bowel incontinence free of charge. However these programs are poorly utilized as reflected in the minority of patients returning for follow-up care: of the 96 patients still alive at the time of the study, 73 (74%) had not returned for follow-up at CCHU. With critical, life-saving follow-up care being offered free of charge, why were the majority of patients languishing without such care in their home villages?

The importance of culture and communication in good outcomes

Understanding the reasons for the poor utilization of follow-up care is crucial to prolonging survival in this group of children. Part of the answer to this quandary is logistical: travel in Uganda is both difficult and costly, making periodic returns to the hospital impractical for many. However, conversations with the caregivers of these patients in their home villages proved to be particularly illuminating in providing insight into the reasons behind the lack of utilization of follow-up care. This author found that most parents simply did not understand the need to return for follow-up care. This in turn stemmed from a general lack of understanding of their child's disease, treatment, or prognosis. The majority of parents had no knowledge of the long-term sequelae of myelomeningocele or of the perils that ensue when these sequelae are left untreated.

Consequently, many caregivers saw no need to invest the time and money to return to the hospital. Furthermore, many were misinformed about their child's prognosis: a number of parents expressed anger that their child was unable to walk, not having been told that the myelomeningocele would render their child irreversibly paralyzed and instead believing that the paralysis was a result of a medical error. This did untold damage to the trust between caregivers and doctors. While some parents held the expectation that their child would walk, others believed that an early death was an unavoidable consequence of disease and consequently abandoned the children with the logic that any resources invested in the child would be wasted. In a culture where great meaning is ascribed to names, the names chosen for these children reflect the hopelessness of these parents: Atoh meaning this child will die, Onono meaning waste of time, or Ajok meaning why has god cursed me. Clearly, failures in communication led to a lack of understanding and misplaced expectations which hampered efforts to provide essential longitudinal care, thereby making a substantial contribution to long-term mortality.

These findings underscore the fact that the education and participation of caregivers in patient care plans are anything but a peripheral concern, particularly in a resource-limited setting such as this. While there is a tendency in situations of scarcity to streamline care by distilling treatment down to its most essential elements in the name of saving more lives, it would be unwise to do so at the expense of long-term survival. Ensuring that caregivers have a vested commitment to the treatment plan is an essential element of treatment, as essential as the initial surgical procedure or longitudinal follow-up care, all of which are necessary for long-term survival.

With all this in mind, the role and the need for community-based rehabilitation is ever more clearly defined. Community-based rehabilitation programs address both of the barriers to the utilization of long-term supportive care identified here. First, they are based in the patient's home communities obviating the need for travel. Second, their constant presence in the community makes them an ideal vehicle for educating caregivers, with the ultimate goal being to make these caregivers vested participants in their child's plan of care. The efficacy of such a model of delivering longitudinal care is demonstrated by the clear and dramatic impact on long-term survival revealed in this study. Collectively, these findings establish the importance and efficacy of community based rehabilitation programs as well as parental understanding and participation in ensuring the long-term survival of children living with myelomeningocele and hydrocephalus in Uganda.

A Shift in Focus and New Initiatives at CCHU

The findings of this study have catalyzed a shift in focus and changes in operational procedure at CCHU. The Hospital celebrated its ten-year anniversary recently, and while the first ten years of operation were characterized by an effort to perform a greater number of procedures each successive year, the findings of this study have shifted attention to ensuring long-term survival after surgery.

Several new initiatives at CCHU aim to improve long-term survival in myelomeningocele patients. To address the lack of understanding among parents about their child's disease and the need for long-term care, the author developed a brief illustrated lecture that is presented to parents of children admitted to the hospital for myelomeningocele closure with time following for discussion and questions. In addition

to explaining the basic pathophysiology of myelomeningocele, the lecture emphasizes the importance of repositioning children to avoid pressure sores, the necessity of follow-up to achieve social urine and bowel continence, and the fact that children with myelomeningocele are capable of growing up to become contributing members of their communities.

With the help of illustrator Bryan Hong (Yale Medical School, Class of 2010), this author created a children's book entitled "Everyone is Different" (Appendix A). This book, which is being reproduced in Uganda and is given to every child admitted for myelomeningocele closure at CCHU, covers the same topics as the parent lecture although from the perspective of a young child living in Uganda coping with the challenges of paraplegia and urinary incontinence. It is our hope that these resources will impress upon children, their caregivers, and their communities that these patients with myelomeningocele are worthwhile individuals capable of contributing to society and deserving of the care and resources to ensure their survival.

As a direct result of the findings reported here, CCHU has begun funding and expanding community-based rehabilitation programs throughout southeastern Uganda in the hopes of replicating the survival benefit identified in this study in communities with community-based rehabilitation programs. In addition, the Hospital has devoted one social worker full time to the task of tracking patients who have missed follow-up appointments to ensure that patients do not fall out of contact with the hospital staff. Enrollment of myelomeningocele patients for a subsequent follow-up study has already

begun at CCHU, with data collection to begin in five years in order to assess the impact of these initiatives on long-term survival.

Conclusions: Practical Barriers to Neurosurgical Care in the Developing World

The finding that five-year mortality is similar between patients treated with ETV and VP shunt implantation fails to support the hypothesized survival benefit for hydrocephalic children in a developing country treated with ETV. However, it would be premature to conclude from this finding alone that there is no actual survival advantage to treatment with ETV in this setting. Taken collectively, the findings from this study demonstrate that long-term rehabilitative care is a far more powerful determinant of mortality than how hydrocephalus is treated or even whether a patient develops hydrocephalus at all. It is entirely possible that there exists a difference in long-term survival between patients treated with ETV and shunt implantation, but that this difference was obscured by the powerful effect of long-term rehabilitative care.

While this study focuses attention on long-term rehabilitative care as the critical determinant of long-term survival in this population, on a broader level it illustrates the profound difficulties of treating neurosurgical disease in a developing country. In Uganda, hydrocephalus is a unique pathophysiological entity accompanied by barriers to treatment which are inconceivable to citizens of developed nations. Understanding these barriers, and the resilient beliefs upon which these barriers are constructed, is critical to

formulating successful approaches to the treatment of disease. This study demonstrates that ignoring these beliefs and barriers comes at the cost of patients' lives.

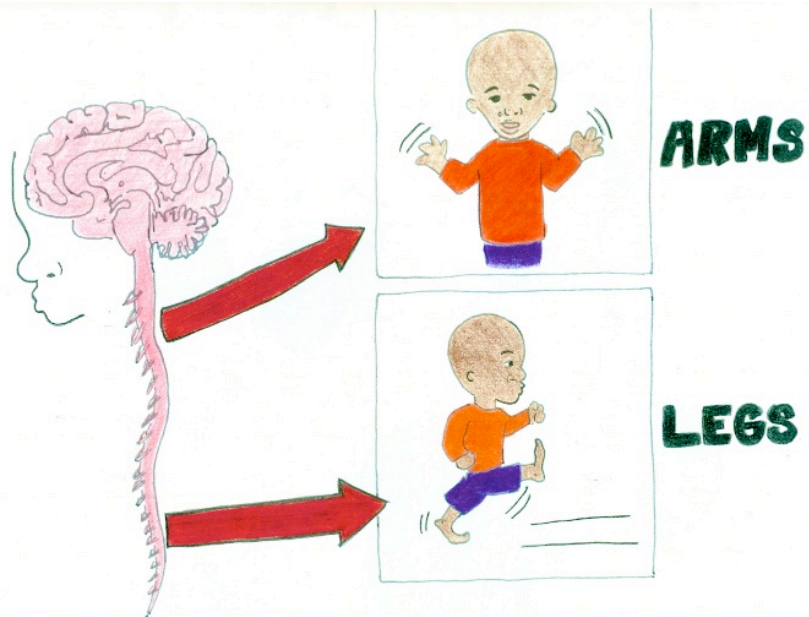
While it is important to acknowledge and understand the profound differences between the developed and developing world, we should not forget the commonalities which transcend cultures and continents. The importance of patient education and participation in treatment plans as an essential component in producing positive outcomes has been demonstrated time and again in the developed world. This is no different in the case of Uganda, and it is perhaps even more important in a setting in which we seek to deliver care across linguistic and cultural barriers. For all of the many differences between Uganda and the United States, one should not forget that some aspects of delivering effective medical care are universal.

The delivery of neurosurgical care to the residents of the developing world is an imperative which cannot be ignored. Adapting a technically complex and technologically dependent field to a developing country is fraught with difficulties, however one must not forget the many practical barriers beyond the operating room which may stand in the way of providing effective treatment. While cultural beliefs and practical barriers to treatment may be considered outside of the purview of neurosurgery in the developed world, these issues must be taken into account if the field of neurosurgery is to provide effective cures in the developing world. Indeed, it is these practical issues of culture and communication which must be considered if we are to ensure that as we advance neurosurgical care in developed nations, that we do not leave the rest of the world behind.

Everyone is Different



Bryan Hong and Ernest Wright



Everyone has a backbone. Inside the backbone is the spinal cord, it tells your arms and legs to move when you want them to.



When I was a little baby, I was different because I had a hole in my backbone. This is called Spina Bifida.



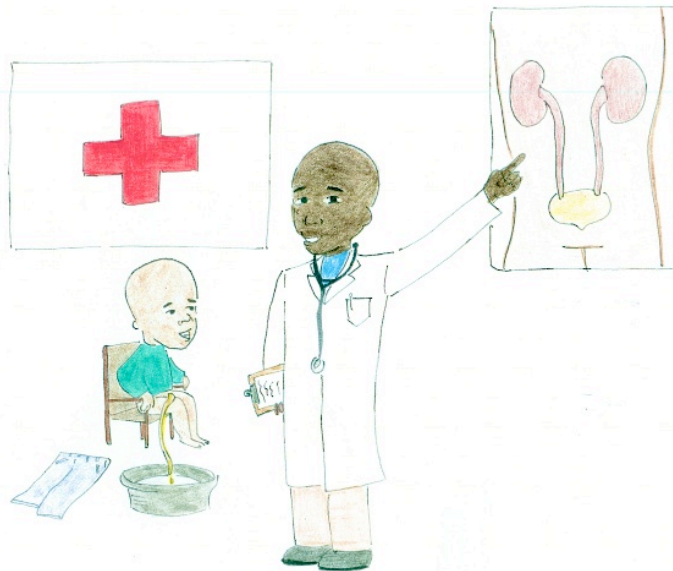
Because of my Spina Bifida, my legs don't listen when I tell them to move. Some children run quickly, some run slowly, and I cannot run at all.



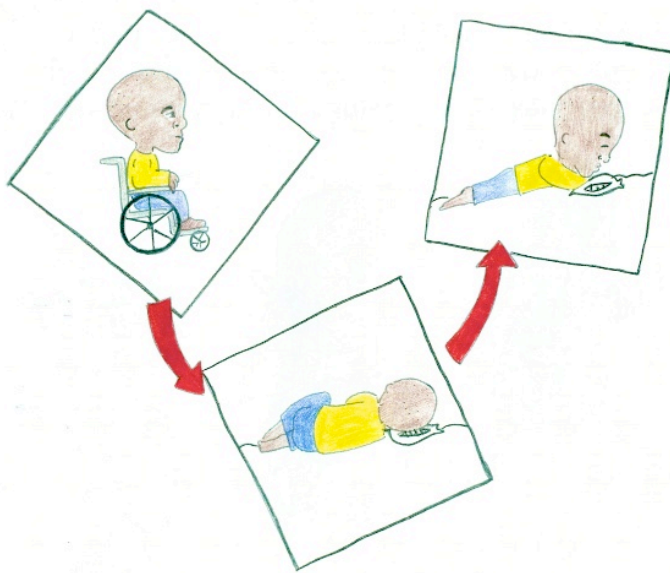
Even though I cannot run, I am good at other things like schoolwork. Everybody is good at different things because everyone is different.



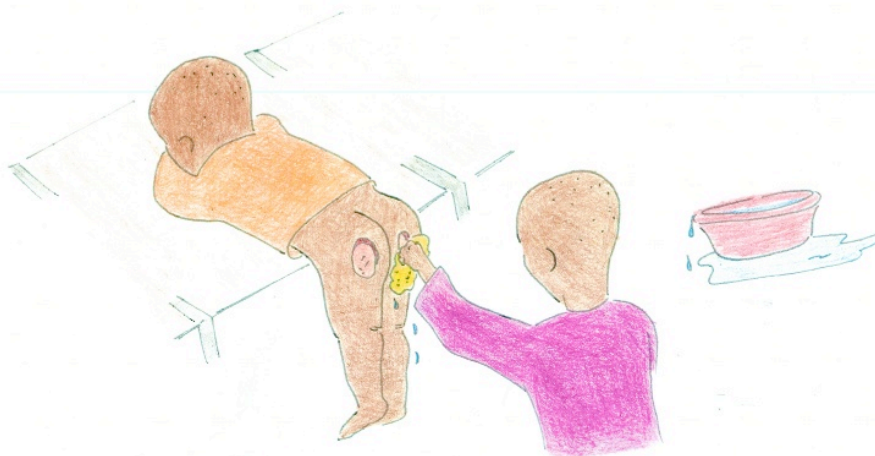
I am different because I cannot control my susu and pupu, even though my friends learned this already. It is not my fault, it is because I have Spina Bifida.



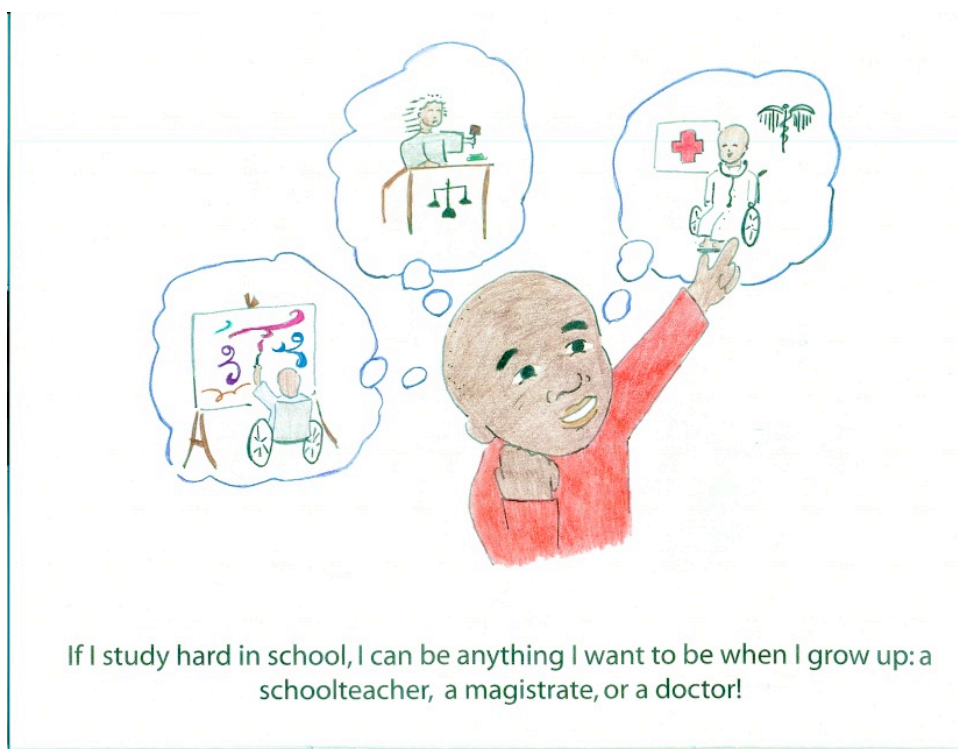
Mama will take me to the health clinic where I will learn how to control my susu and pupu.



I am different from my friends because I cannot sit on my bottom for more than one hour or I will get a sore. I have to lay on my side or on my belly at least ten times a day.



If I do get a sore on my bottom, mama helps me keep it clean by washing it with soap three times a day. I cannot sit on my bottom, I have to lie on my side or on my belly until the sore gets better.





I am different, just like everyone is different in their own way.

My mama loves me because I am different.

I am perfect, just the way I am.

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