

Original Article

The International Tethered Cord Partnership: Beginnings, process, and status

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Abstract

Background: Spina bifida presents a significant cause of childhood morbidity in lower- and middle-income nations. Unfortunately, there is a paucity of literature examining outcomes among children with spina bifida in these countries. The goal of the International Tethered Cord Partnership is twofold: (1) to establish an international surveillance database to examine the correlation between time of repair and clinical outcomes in children with spina bifida and tethered cord; and (2) to foster collaboration among international institutions around pediatric neurosurgical concerns.

Methods: Twelve institutions in 7 countries committed to participating in the International Tethered Cord Partnership. A neurosurgeon at each institution will evaluate all children presenting with spina bifida and/or tethered cord using the survey instrument after appropriate consent is obtained. The instrument was developed collaboratively and based on previous measures of motor and sensory function, ambulation, and continence. All institutions who have begun collecting data received appropriate Institutional Review Board approval. All data will be entered into a Health Insurance Portability and Accountability Act (HIPAA) compliant database. In addition, a participant restricted internet forum was created to foster

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communication and includes non-project-specific communications, such as case and journal article discussion.

Results: From October 2010 to December 2010, 82 patients were entered from the various study sites.

Conclusion: To our knowledge this is the first international pediatric neurosurgical database focused on clinical outcomes and predictors of disease progression. The collaborative nature of the project will not only increase knowledge of spina bifida and tethered cord, but also foster discussion and further collaboration between neurosurgeons internationally.

Key Words: International database, spina bifida, tethered cord

INTRODUCTION

One of the many clinical problems that neurosurgeons from developing nations face is that of implementing the standard of care from high-income countries (HIC) for myelomeningocele and other surgical forms of spina bifida. This issue is relevant because myelomeningocele is significantly more frequent in developing nations. While we accept as a fact that early closure of myelomeningocele improves survival by decreasing infection and may possibly improve clinical outcomes, there are no comparative data about this issue and for understandably ethical reasons will never be carried out. The development of a multicenter international database will provide the data to improve our understanding of the outcomes of children with delayed repair. An improved understanding of spina bifida and tethered cord will allow international institutions to improve care for affected children.

Additionally, it goes without saying that in the current age, the internet is an invaluable means of communication. One of the major strengths of a project-based internet site is that it can foster a greater sense of ownership among project participants, affording all participants equal say in the research process. Thus, the research becomes the responsibility of all and the property of none.

In order to do so, we must demonstrate that early repair of spina bifida does indeed improve patient outcome. To date, no large patient data from delayed spina bifida repair has been analyzed to correlate outcome with time of repair. In order to improve our understanding of the pathophysiology of delayed myelomeningocele repair we partnered with various centers in 7 countries. On a related note, the question of the optimal timing for tethered cord repair was raised by many neurosurgeons as they cited the lack of conclusive documentation of the true natural history of tethered cord.

The results of this project are of interest to pediatric neurosurgeons around the world. Although the results will be reported in approximately 1–2 years from now,

we wanted to share the rationale and method utilized to suggest this particular approach for many of the clinical problems that affect patients with neurosurgical disorders in developing countries. The insight into various pathologies will benefit patients from any country.

MATERIALS AND METHODS

Twelve institutions in 7 countries committed to the project and submitted letters of support for the International Tethered Cord Partnership (ITCP) [Table 1]. All institutions have either fulfilled all the Institutional Review Board (IRB) requirements at their own institution and have submitted approval to UCLA IRB or are in the process of acquiring institutional approval.

All patients identified with spina bifida and tethered cord between 0 and 15 years of age at collaborating institutions will be included in one centralized database. All patients with spina bifida and/or tethered cord will be included in the ITCP database at the time of presentation to the neurosurgical service at each hospital and will be followed at 1-year intervals. Follow-up will be conducted at standard outpatient clinic visits every year per standard of care for a period of no less than 5 years. Because most neurosurgeons will see these patients at yearly intervals independent of the study, we do not expect significant loss to follow-up. Patients seen at clinic appointments at each institution will be consented for inclusion in the study. Inclusion criteria include all live births with myelomeningocele, meningocele, sacral lipoma, and occult spinal dysphrasim. Exclusion criteria include anencephaly, caudal regression, encephalocele, and rachi-schisis.

A contact neurosurgeon at each institution will fill out the survey at each clinic visit with all children with spina bifida seen during the study period. In addition, if photographs of the lesion/defect were taken, the patient will be asked for permission to use the photographs without any identifying information for the study purposes.

Table 1: Participating Institutions

Country	City	Institution	Coordinator
Argentina	Buenos Aires	Children's Hospital Ricardo Gutierrez	Santiago Portillo, MD
	Buenos Aires	Pediatric Hospital Garrahan	Fernando Contreras, MD
China	Shanghai	Shanghai Children's Medical Center	Bao Nan, MD
	Shenyang	China Medical University	Hongyu Zhao, MD Yunhui Liu, MD
Guatemala	Guatemala City	St. John's General Hospital	Graciela Mannucci, MD
	Guatemala City	Research Center for Health Sciences, University of San Carlos, Guatemala	Erwin Calgua, MD
Mexico	Culiacan	Culiacan General Hospital	Dulce Espinoza, MD
	Merida	High medical specialty unit of the social security Institute of Mexico	Jose A. Hoil, MD
	Guadalajara	Civil Hospital of Guadalajara	Juan Luis Soto-Mancilla, MD
Nicaragua	Managua	Manuel de Jesus Rivera "La Mascota" Pediatric Hospital	Juan Bosco Gonzalez, MD
Nigeria	Ile-Ife	Obafemi Awolowo University	Edward Komolafe, MBBS
Panama	Panama City	Children's Hospital	Guzmán Aranda, MD

The survey was guided by previous studies examining ambulation, continence, and sensory and motor function in patients with spina bifida in accordance with spina bifida standard of care in the United States. Neurosurgeons at each institution reviewed the instrument to determine if the desired information could be gathered from the patient charts easily. The instrument sought to characterize the patient's neurosurgical history, motor and sensory function, ambulation ability, and continence. In addition, several demographic questions are included in the first portion of the survey to better characterize the patient population.

The survey instrument was translated into Mandarin by a native speaker of Chinese fluent in English. It was then reviewed by the neurosurgeon in China for comment. The principal investigator translated the instrument into Spanish. The Spanish version was then reviewed by a neurosurgeon in Nicaragua and a neurosurgeon in Mexico (both native Spanish speakers).

Website

Using 37signals Backpack internet application, we have created an intranet portal where researchers from around the globe can easily collaborate and share information. Additionally clinicians will be able to contribute cases to be included in the study using an online web formed secured with 1024-bit SSL encryption. Cases will be stored in Linux servers using advanced database encryption built upon the MySQL database server to ensure security of patient information. Both the intranet and database will be accessible through the new itpartnership website. The website features an advanced Content Management System, which allows both staff and researchers to quickly update the public on developments on projects. This Content Management System is managed by a cluster of Linux virtual servers and load balanced to provide users with a quick quality web experience.

Analysis

Statistical analyses will focus on the multivariate relationships between level of lesion, type of lesion, time of repair, and outcomes, including motor and sensory function, ambulation, and continence. Proportions will be expressed as percentages and continuous data as medians with interquartile and robust ranges. Continuous and categorical data will be compared using the Wilcoxon and Fischer's exact tests as appropriate, and additionally by robust procedures to control for statistical outliers. Two-tailed tests of significance will be used, with a *P* value of 0.05 considered significant. Predictive models for dichotomized outcomes at follow-up will be obtained by mixed models analysis and by generalized additive modeling. Covariates will be added to the models singly to seek the largest decrease in the Akaike Information Criterion. For covariates involving time, each will be entered into the model for evaluation of trends, and computed as odds ratios for good outcome at follow-up related to time and related to patient age, with 95% confidence intervals. Cross-facility comparisons will be done with additional covariates, including selected regional sociodemographic parameters. In each instance, patients with missing data in any covariate will be excluded from the modeling process. All statistical computations will be done using the international open-source collaborative tools in R: A Language and Environment for Statistical Computing 2010 (R Foundation for Statistical Computing, Vienna, Austria), including mcg, lmer, and related packages.

Although the number of cases seen at the institution varies, discussions with the neurosurgeons from Nicaragua, Guatemala, and China suggest that each site will be able to contribute at least 100 cases each year. Based on previous internal reviews, one site in Guatemala (Hospital General San Juan de Dios) reported an average of 15–20 cases of spina bifida per month, whereas

Nicaragua reported an estimated 10–15 cases per month. China has reported up to 30 cases per month.

Preliminary results

To our knowledge this is the first international pediatric neurosurgical database focusing on clinical outcomes and predictors of disease progression. At the time this article was written, the database had reached 82 patients (collected between October 2010 and December 2010). In addition to the patient data, the project website is launched. The restricted access website consists of case discussions and journal articles posted by members of the ITCP.

DISCUSSION

The prevalence of spina bifida in lower- and middle-income countries (LMIC) is significantly higher than that in high-income nations, such as the United States and represents a significant source of childhood morbidity worldwide. The incidence of spina bifida in China is about 149.0 per 10,000 live births vs 1.9 per 10,000 live births in the United States.^[2,11] Additionally, the World Health Organization (WHO) estimates that spina bifida aperta accounts for 1488 disability adjusted life years (DALYs) in LMIC compared with 63 DALYs in HIC.^[12] In the United States, a child born with spina bifida aperta (or myelomeningocele) is referred to a medical center where the newborn can receive specialized neurosurgical care within 24 h of birth. This practice is based on literature that has shown that earlier repair may lead to decreased mortality and limb paralysis.^[3,6,15] In 1967, Sharrard *et al.* demonstrated that closure within 24 h of birth in a group of 526 patients with myelomeningocele resulted in reduced 3-year mortality and improved lower limb function. However, in their analysis, time of repair was defined as a categorical variable and not continuous. As such, children whose defect was repaired on the fifth day of life were grouped with children who were never operated on. This prohibited them from determining if patients within that group would have benefited from delayed treatment. Furthermore, the author's did not examine the correlation between lesion, time of repair, and multiple outcomes.

Another study by Heimburger *et al.* conducted between 1950 and 1955 found that walking and sphincter control (defined as normal or abnormal) were improved in children whose defect was repaired before 24 h after birth or after 1 month.^[7] However, this study included a small number of operated patients (n=71) and only examined walking and sphincter control in 37 patients. They did not have enough patients to measure time of repair as a continuous variable nor chronicle the progression of symptoms quantitatively in either the surgical or nonsurgical patients. Of note, case ascertainment in both these studies comes into question. In the

Heimburger study, they did not state whether the cases were open or closed defects, whereas in the Sharrard study they included rasheschisis. Additionally, neither study addressed nonoperated patients who were older than 36 months in depth. Partially as a result of the 2 studies described above, standard of care in the United States now dictates that surgical repair occur within 24 h of birth. However, this may not be feasible in certain international circumstances. These circumstances include, but are not limited to, economic restrictions and lack of awareness of the benefits of early intervention in the community.^[1,8] As such, early repair of spina bifida is not standard in LMIC and thus there is a large and constantly increasing population of children with unrepaired spina bifida aperta in LMIC. Considering the weight of economic factors we do not pretend to impose the standard of care of nations with more resources. But by working together with physicians who care for those children we can define treatment time frames within which the expected neurological damage can be halted.

Academic medicine has not been able to elaborate guidelines for prevention of neurological deterioration that can be applicable to the reality of a patient born in LMIC because there is no large body of data about patients whose spina bifida was repaired months after birth. In spite of the high incidence of spina bifida in these countries, there is a paucity of literature examining outcomes among children with unrepaired spina bifida. Furthermore, the results from HIC should not be generalized to patients in LMIC. To our knowledge, there is no literature characterizing the average time to repair internationally and there are limited studies comparing outcomes in terms of ambulation, continence, and motor and sensory function both internationally and in the United States with regard to time to repair. As such, it is imperative that we understand the relationship between timing of repair and outcomes in an international setting. This can be used to shape international surgical guidelines and build appropriate infrastructure at institutions in order to optimize long-term outcomes for patients born with spina bifida.

In HIC, we see patients who develop symptomatic tethered cord years after myelomeningocele repair (between 3% and 15% of children will exhibit symptoms of tethered cord) with clear indications for surgery.^[14] Phuong *et al.* retrospectively examined the natural history of tethered cord in a group of 45 patients with repaired myelomeningocele with a mean follow-up period of 12.5 years. In this group of patients, symptoms of tethered cord, such as bladder spasticity and contractions, were treated symptomatically only and no patient underwent an untethering procedure. They found that 88.9% of patients required further orthopedic or urologic procedures due to continued symptoms. As such, it seems reasonable to presume that unoperated

myelomeningocele will also present with symptoms of tethering. However, there is little literature examining the role of tethered cord in unrepaired myelomeningocele.

Although the degree of improvement varies following untethering and is multifactorial, patients with evidence of neurogenic bladder, scoliosis, and/or worsening orthopedic deformities that cannot be explained by some other etiology are usually repaired in the United States. As such, the literature chronicling the natural history of tethered cord in the United States is generally limited to small retrospective sample sizes. Among these studies, it has been shown that symptomatic tethered cord will produce clinical deterioration with regard to bladder spasticity and orthopedic foot deformity if only treated symptomatically.^[4,14] However, controversy still surrounds the repair of asymptomatic tethered cord.^[4,9] Currently, there is no overwhelming consensus to untether asymptomatic tethered cord early in life.^[10] Additionally, studies have largely failed to elucidate which patients are more likely to develop progressive tethered cord symptoms. Studies have not yet identified any patient characteristics that predict tethered cord progression. Recent studies have failed to confirm an association between lumbosacral angle and progressive tethered cord but this may be limited due to small sample sizes in several studies.^[5]

Furthermore, there is a lack of literature from LMIC examining the natural history of tethered cord or the impact of timing of surgical repair on the outcomes discussed above. As such, results from a large international database of tethered cord may help us better understand the natural history of tethered cord and help shape guidelines in LMIC.

Further support for the need for this partnership stems from the Institute of Medicine (IOM) strategies to reduce the burden of brain disorders in developing countries.^[13] One strategy they suggested was to “increase public and professional awareness and understanding of brain disorders in developing countries, and intervene to reduce stigma and ease the burden of discrimination often associated with these disorders.” In order to do so, we must have an accurate estimation of the status of such disorders in each country. This partnership will help characterize the problem in each country to raise awareness and provide physicians the data to petition ministries of health for appropriate allocation of resources. A second strategy the IOM suggested was to “create national centers for training and research on brain disorders in developing countries. Link these centers with institutions in HIC through multicenter research projects, staff exchanges and training, and Internet communication.” The ITCP embodies this strategy. The database will serve not only to fill in the gaps in current knowledge, but also to create training opportunities for international physicians. Physicians will be connected to

research and training opportunities through the network of participating researchers and will be granted access to funds for training and research. The International Tethered Cord Partnership exemplifies these strategies as not only does it partner multiple institutions from around the world in research, it also ties physicians together through a collaborative website. In addition to the data entry component of the website, participating institutions will be able to log in to a forum to discuss cases and journal articles posted monthly. This will facilitate international discussion on topics related to spina bifida and tethered cord.

Unfortunately, there is a wide gap in the number of resources available for treating neurosurgical diseases between LMIC and HIC. Strategies for bridging the divide have taken many forms, all of them with their imperfections but all of them well intended. Neurosurgical relief efforts have adopted different tactics. These efforts range from individuals or groups who travel to provide surgical care to exemplary organizations, such as the Foundation for International Education in Neurological Surgery (FIENS). This organization is exemplary in that it cares not only for service but also for the education of neurosurgeons in the host nations.

Surgical Neurology International is a proof of a trend toward valuing the voice of the neurosurgeons that have to rely more on clinical acumen than on sophisticated diagnostic testing. We who practice in the privileged environment of abundant resources can learn from their insight. The wealth of the experience of our colleagues from developing nations is not only based on their cunningness to correlate pathophysiology with limited imaging but also on the vast clinical experience that they acquire in spite of the different proportion of clinicians per population. The majority of patients in developing nations seek medical care in a limited number of public hospitals.

The prevailing concept of our proposed approach is creating a forum controlled by the participants, limited to a single pathology. This forum will provide a place for the much maligned anecdotal evidence that does not often find its way into current publications. The partnership and database will be a constant work in progress and be shaped by the participants.

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