Call for Collaboration: Characterization of a Multicenter Hydrocephalus Shunt Biobank

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Research

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Abstract

Background

Pediatric hydrocephalus is a devastating and costly disease. The mainstay of treatment is still surgical shunting of cerebrospinal fluid (CSF). These shunts fail at a high rate and impose a significant burden on patients, their families and society. The relationship between clinical decision making and shunt failure is poorly understood and multifaceted, but catheter occlusion remains the most frequent cause of shunt complications. In order to investigate factors that affect shunt failure, we have established the Wayne State University (WSU) shunt biobank.

Methods

To date, six hospital centers have contributed various components of failed shunts and CSF from patients diagnosed with hydrocephalus at a young age. The hardware samples are transported in paraformaldehyde and transferred to phosphate-buffered saline with sodium azide upon deposit into the biobank. Once in the bank, they are then available for study. Informed consent is obtained by the local center before corresponding clinical data are entered into a REDCap database. All data are entered under a coded identifier. Collaborators may then correlate biologic findings against the clinical database.

Results

295 shunt samples were collected from 228 patients starting from May 2015 to September 2019. Patients with multiple samples in the bank provide a unique opportunity to study longitudinal changes in disease. With the clinical data alone, we saw a significant difference in the number of revisions per patient between centers (Kruskal-Wallis H test, p-value= 0.000022). There was no significant difference between the distributions of hydrocephalus etiologies between centers, and the leading etiology at all centers was post-hemorrhagic hydrocephalus.

Conclusion

Hospital center and patient recruitment for the biobank is ongoing. The biobank will yield insights for future collaborators, allow centers to benchmark their performance, and offer a unique-longitudinal perspective on the pathology of this lifelong condition. Future work will expand on the contribution of different site-specific and patient-specific factors to identify potential cause and effect relationships.

Background

Hydrocephalus, a condition caused by altered cerebrospinal fluid (CSF dynamics), affects approximately 1 in 1,100 people in the USA. The perturbation of CSF homeostasis can lead to increased ventricular size and compression of vital brain structures. There are a variety of hydrocephalus etiologies. Those most common in pediatrics include congenital central nervous system (CNS) malformations, infection, intraventricular hemorrhage (IVH), genetic defects, trauma, and teratogens. Risk factors associated with
pediatric hydrocephalus include birth weight less than 1,500 grams, prematurity (gestational age less than or equal to 30 weeks), maternal diabetes, low socioeconomic status, and male sex. Incidence is lower in Asians than other races.\textsuperscript{4, 5}

Shunting of CSF from the ventricles became the mainstay of treatment in the 1950s, with ventriculoatrial shunts (VAS) being the preferred configuration. Shunts utilizing valves for CSF pressure or flow control soon became the norm. In the 1980s the VAS was superseded by the ventriculoperitoneal shunt (VPS) for hydrocephalus management. In the 1990s endoscopic third ventriculostomy (ETV) became an option to manage some types of obstructive hydrocephalus, obviating the need for fallible shunt hardware.\textsuperscript{6} In 2005 and again in 2012, the National Institutes of Health sponsored an expert panel to discuss priorities for hydrocephalus research, this panel concluded both times that current methods of diagnosis, treatment and outcome monitoring need improvement.\textsuperscript{20, 21} More recently, the Hydrocephalus Clinical Research Network, a consortium of 14 North American Pediatric Hospitals, developed a standardized operating protocol that was shown to reduce rates of post-operative infection associated with shunt procedures.\textsuperscript{7}

CSF shunt systems have a failure rate of up to 85% within 10 years from initial insertion.\textsuperscript{8, 19} Annual hospitalizations for hydrocephalus have reached 70,000 per year in the USA. Nearly all patients with hydrocephalus (98%) will experience shunt failure in their lifetime.\textsuperscript{9} Pediatric patients experience higher rates of failure, with 40% of shunts failing within 2 years of implantation.\textsuperscript{10} The annual cost of pediatric hydrocephalus intervention is approximately $195.5-204.5 million\textsuperscript{11} and the overall burden to the healthcare system is between $1.4-2.0 billion; over half of these expenses are due to shunt revisions.\textsuperscript{12}

Tissue obstruction of the proximal (i.e. ventricular) catheter is the main source of failure in VPS systems, accounting for approximately 50% of failures within the pediatric population.\textsuperscript{22} The mechanisms underlying this failure are still poorly understood. Sekhar et al. (1982)\textsuperscript{23} provided the earliest description of the cell types involved in shunt catheter occlusion, and more recent efforts have shown that astrocytes and microglia likely play a central role in this tissue obstruction.\textsuperscript{13} The molecular pathways underpinning this phenomenon, which could serve as targets for pharmacologic intervention, are not yet known. Likewise, there is a lack of understanding as to how clinical decision-making influences shunt failure rates. With the new opportunities offered by cheaper sequencing and tissue-clarification, the field stands poised to gain a deeper understanding of the biological processes underlying shunt failure due to obstruction. To facilitate investigation of this question, we created a national biorepository of all failed shunt hardware, following other institutions that have created biobanks for different medical conditions.\textsuperscript{24, 25} Centered at Wayne State University (WSU), this shunt biobank and corresponding clinical database has the potential to be a global cohort of explanted central nervous system hardware. We are conducting our own studies on samples with current collaborators, but it is our hope and intent to invite more collaborators to use the biobank for their research. By having a well formatted database, we hope that it will serve as a pipeline for future retrospective studies to enhance translation of biologic investigations and improved treatment paradigms.
Materials And Methods

Ethics Approval and Study Population:

The permission to collect failed and explanted shunt samples was approved by local ethics committees at each participating center; records of approval were sent to the coordinating center, WSU, and submitted as amendments to our protocol under Institutional Review Board (IRB). Written informed consent was obtained from all patients or their legally authorized representative. Collection was performed in a manner consistent with the Declaration of Helsinki and represents no modification to the standard of treatment. The patient population includes a vulnerable group (children), but the study is aimed at addressing the health needs of this group and cannot be conducted in a non-vulnerable group. The biobank has samples from individuals who at the time of sample removal were aged between 36 days and 42 years. Samples were collected from individuals with any hydrocephalus etiology and clinical history. Patients were evaluated by local centers according to their individual guidelines, and samples were only collected if the shunt malfunction indicated surgical intervention.

Current Centers:

Children's Hospital of Michigan and Wayne State University (WSU), St. Louis Children's Hospital and Washington University School of Medicine in St. Louis (WUSM), Texas Children's Hospital -Baylor College of Medicine (TEX), Riley Children's Hospital – Indiana University Health (RC), the Children's Hospital of Alabama at University of Alabama Birmingham (ALA), and John's Hopkins Medicine (JHU).

Sample Collection:

After removal by a surgeon, the shunt samples were placed in a solution of sterile 4% (w/v) paraformaldehyde (PFA). They were then given a unique identifier and deidentified to those who performed the analyses. Samples were shipped to the coordinating center at room temperature. Upon arrival, the shunt components were changed to a solution of 1X PBS with 0.01% (w/v) Sodium Azide and stored at 4 °C. The solution was refreshed monthly. If CSF was collected, the time elapsed between collection and processing was noted. The CSF was kept below 4 °C until it was spun down at 1000 g for 6 minutes. The supernatant was then aliquoted into 1.5 mL Eppendorf polypropylene microcentrifuge tubes. The supernatant was stored at -80 °C and the cell pellet was stored in liquid nitrogen.

The clinical data collected includes: hydrocephalus etiology, date of birth, sex, race and ethnicity, history of endoscopic third ventriculostomy (date of procedure, reason for failure if applicable), date of surgery/sample collection, weight, cause for hardware removal, CT or MRI collected, positive CSF culture during admission, physician performing procedure, hardware types included in sample, date of hardware implant, type of shunt system, whether the catheter was adherent to a ventricular wall or the choroid plexus, number of holes on the catheter (if applicable), intraluminal- electrocautery used in sample procurement, hardware brand, surgical approach used when failed hardware was inserted, number of prior revisions, number of revisions without hardware change, number of ventricular catheters, number of
ventricular catheter obstructions, number of peritoneal catheters, number of atrial catheters, number of valves, number of external ventricular drains (EVD), number of reservoirs (including subgaleal vs. ventricular type), number of intracranial pressure (ICP) monitors, prior shunt types, and the dates at which shunt types were switched.

Statistical Analysis:

SPSS for Windows version 25.0 was used. The chi-square test was used to check for potential differences in race between patients and census data for the metropolitan areas where our centers are located. The nonparametric Kruskal-Wallis test was used to determine if statistically significant differences existed between study groups. Dunn's post hoc test was used for pairwise comparisons. A generalized linear model using gamma with log-link was employed for regression analysis, deviance residuals were checked for normality.

Clinical Database:

Study data were collected and managed using REDCap electronic data capture tools hosted at Wayne State University. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Each participating center is responsible for the collection and maintenance of their data. All centers can access the entirety of the clinical data in our REDCap database.

Results

Center enrollment:

We are currently recruiting more centers to take part in the biobank. Figure 1 demonstrates the process by which a new center is enrolled. Before a principal investigator contacts us, they should confirm that a clinical coordinator or research assistant on their team has time available to conduct the retrospective chart review and data entry for each patient from whom a sample is collected. Additional responsibilities of a center include training personnel to prepare the samples and send shipments. Once it has been established that the new center has the personnel resources to join, we provide them with a copy of the IRB proposal so that they may submit a version to their local ethics board. Next, material transfer agreements (MTA) are filled out with both the new center and WSU. Many local centers require separate MTAs for the clinical data and the shunt samples. Next, the new center often requires a data usage agreement to be completed. Finally, once WSU has a record of the new center's IRB approval and the MTAs on file, we submit an amendment to our IRB protocol to add the new center.

Once the center is enrolled, we provide training to the personnel assigned to the project. This training includes how to use REDCap and a detailed explanation of all variables being collected. We also provide logistic support, sterile PFA, and sample containers. We conduct reviews of the database in a quality control effort to catch potential mistakes before they have been repeated.
We have formal agreements with 6 centers currently in place. The data in this paper comes from 4 centers: WSU, WUSM, TEX, and RC. The other centers, ALA and JHU, had not contributed samples at the time of analyses. Even if a center is unable to provide the clinical data associated with shunts, we invite centers to send us failed shunts that would otherwise be discarded. These samples can be used in testing new reagents and methods.

Current Biobank Content:

Across these 4 centers, to date we have enrolled 228 patients, from whom 295 samples have been collected (Table 1); the majority come from WSU and WUSM. 221 out of 295 (74.9%) samples collected contain a proximal catheter. 75 samples include a proximal catheter and another shunt component, while 146 are proximal catheters alone. We also have several subdural-catheters, EVDs, valves, reservoirs, peritoneal catheters, atrial catheters, and lumbar catheters. We have CSF associated with 76 samples, the entirety of which is from WSU and WUSM.

| Table 1: Types of Samples in the Biobank | Center |
|-----------------------------------------|--------|
|                                         | WSU    | WUSM  | TEX   | RC    | Total |
| Number of patients                      | 73     | 109    | 34    | 12    | 228   |
| Number of samples                       | 115    | 132    | 34    | 14    | 295   |
| Number of samples associated with CSF   | 40     | 36     | -     | -     | 76    |
| Mean samples per patient                | 1.58   | 1.21   | 1.00  | 1.17  | 1.29  |
| Sample Breakdown By Hardware Type       |        |        |       |       |       |
| Ventricular catheter only               | 100    | 13     | 26    | 7     | 146   |
| Valve only                              | 1      | 18     | 3     | 1     | 23    |
| Peritoneal catheter only                | 1      | 4      | 3     | -     | 8     |
| Other (reservoir only, EVD only, other combinations) | 13       | 97     | 2     | 6     | 118   |
| Samples which include a ventricular catheter | 101     | 81     | 28    | 11    | 221   |
| Number of samples per year              |        |        |       |       |       |
| 2015                                    | 1      | 24     | -     | -     | 25    |
| 2016                                    | 49     | 15     | -     | -     | 64    |
| 2017                                    | 32     | 27     | 1     | -     | 69    |
| 2018                                    | 28     | 37     | 23    | 1     | 89    |
| 2019                                    | 5      | 29     | 10    | 13    | 57    |
The demographics of the patients already enrolled (Table 2) show a prevalence of males; however, this was not statistically significant. The total percentage of African American patients was significantly different when compared to the general population (chi-square p = 0.001291); however, this significance disappears when controlling for the percentage of African Americans in the metropolitan areas our hospitals serve (chi-square p = 0.827754). Patient age was significantly different between the sites (Kruskal-Wallis H test p = 0.000003).

| Table 2: Demographics of Patients with Samples in the Biobank | Center |
| --- | --- | --- | --- | --- | --- |
|  | WSU | WUSM | TEX | RC | Total |
| **Biologic Sex** | | | | | |
| Male | 45 | 53 | 21 | 5 | 124 |
| Female | 28 | 54 | 13 | 7 | 102 |
| Other | - | 2 | - | - | 2 |
| **Race** | | | | | |
| White | 32 | 89 | 29 | 9 | 159 |
| African American | 34 | 16 | 5 | 2 | 57 |
| Asian | 2 | - | - | - | 2 |
| American Indian/Alaska Native | - | - | - | - | - |
| Native Hawaiian or Other Pacific Islander | - | - | - | 1 | 1 |
| Declined/Unknown | 5 | 4 | - | - | 9 |
| **Ethnicity** | | | | | |
| Hispanic or Latino | 1 | 1 | 16 | 1 | 19 |
| Not Hispanic or Latino | 67 | 104 | 18 | 11 | 200 |
| Declined/Unknown | 5 | 4 | - | - | 9 |
| **Average Age at Sample collection (in years +/- SD)** | 12.12 (+/- 10.39) | 6.50 (+/- 6.09) | 11.00 (+/- 5.73) | 6.90 (+/- 5.13) | 9.23 (+/- 8.39) |

Hydrocephalus History:

The most common hydrocephalous etiology (Fig. 2a) in our patient cohort was post-hemorrhagic hydrocephalus of prematurity (95 patients, 41.9%), followed by myelomeningocele (37, 16.2%), aqueductal-stenosis (18, 7.9%), brain tumors (15, 6.6%), congenital CNS malformations (12, 5.2%), communicating congenital (11, 4.8%), other (8, 3.5%), trauma (7, 3.1%), postnatal meningitis (6, 2.6%), Dandy-Walker malformation/obstructive arachnoid cyst (6, 2.6%), unknown (6, 2.6%), and congenital CNS infection (3, 1.3%). Ventriculomegaly without CNS abnormalities, craniosynostosis and pseudotumor cerebri were all under 1% of patients.
The causes for removal of the samples (Fig. 2b) are as follows: proximal catheter obstruction (121 samples, 41.2%), other (39, 13.2%), multiple reasons for removal (37, 12.5%), externalization due to infection (26, 8.7%), internalization i.e. EVD removal (20, 6.9%), valve obstruction (10, 3.5%), distal catheter obstruction (9, 3.1%), disconnection (7, 2.4%), over-drainage (6, 2.1%), truncated catheter (4, 1.4%), reservoir malfunction (4, 1.4%), and unknown (4, 1.4%). Ventriculomegaly not otherwise specified, fracture of the proximal catheter, externalization due to pseudocyst, and externalization due to other cause were the cause of removal for less than 1% of samples. Samples were placed in the ‘Multiple reasons for removal’ category when the multiple causes existed without being able to determine the root cause of the failure. Including the occurrences when there were multiple potential causes of shunt failure, 45.2% of samples were removed due to proximal catheter obstruction. Common causes grouped under ‘Other’ are switching a reservoir to a VPS, pressure sores/irritation, and wound dehiscence. When the indication for failure included infection, we cross referenced lab results to check if the patient had a positive CSF culture during their admission. Out of the 29 samples that were removed for suspected infection: 6 had negative CSF cultures, 20 had positive cultures and no cultures were ever obtained for 3. Additionally, 4 others in whom infection was not suspected pre-operatively showed positive CSF cultures.

The number of revisions prior to patient enrollment in the biobank (Fig. 2c) differed significantly between centers (Kruskal-Wallis H test p = 0.000022); the medians (and interquartile ranges) are as follows: WSU 3 (8), WUSM 1 (3), TEX 1 (1), and RC 1 (4). Pairwise comparisons (Dunn's post hoc test) showed WSU to be significantly higher than TEX and WUSM (p = 0.003 and p < 0.000 respectively). All other comparisons were not significant. Given that age significantly varied between the centers, regression analysis was performed to test if this relationship persisted when controlling for age. Center significantly impacted the number of prior revisions even when controlling for age (p = 0.017). The number of ventricular catheter obstructions prior to enrollment (Fig. 2d) was also significantly different between centers (Kruskal Wallis H test p = 1.8241^{-14}). Pairwise comparison (Dunn's post hoc test) showed WUSM to be significantly lower than TEX and WSU (p < 0.000 and p < 0.000 respectively). All other comparisons were not significant. Regression was also performed to test if this relationship persisted when controlling for age: it was found that center significantly (p = 0.00057) affected the number of ventricular catheter obstructions when controlling for age.

One other metric by which centers can be compared is the mean length of time that each ventricular catheter was implanted before failing (Fig. 3). The median lengths of insertion in months (and interquartile ranges) were as follows: WSU 5.84 (52.08), WUSM 8.97 (64.54), TEX 8.61 (55.16), and RC 8.01 (42.48). There was not a significant difference between the centers (Kruskal-Wallis H test p = 0.609).

**Discussion**

Given the diversity of etiologies and the many reasons for failure, a shunt biobank is an essential tool in the effort to understand hydrocephalus pathology and outcomes. The availability of high-quality samples associated with clinical data will support future translational programs by ourselves and collaborators. The usage of a REDCap database allows for data security and seamless sharing to collaborators.
To address some of this variability, we have categorized shunt failure quite specifically, rather than binning failure into “Obstruction” and “Non-Obstruction”. We favor specifications such as where an obstruction or fracture occurred (through gross and microscopic investigation) and if there was a suspected infection. Given prior studies demonstrating that microglia and astrocytes compose the majority of tissue obstructing proximal catheters\textsuperscript{13,16}, we believe that infection and other inflammatory processes may be important variables for future studies. A deep understanding of these processes, how they relate to clinical factors, and the interaction of these parameters will play into identifying how and why shunts fail and, in future work, prediction of shunt outcome.

One result that surprised us was how the number of revisions per patient (revision history) varied between centers when controlling for age, but that the relationship between center and length of implantation did not. We hypothesized that there would be an inverse relationship between age-controlled number of revisions and length of implantation. Trends show WSU to have an older skew of patients, some of whom developed hydrocephalus later in childhood. When controlling for number of years with a shunt system rather than age, trends showed WSU to have fewer revisions per year of shunt implantment. The WSU patients with longer implant durations can serve as the basis of future investigation to identify factors which contribute to the success of their shunts. A genomic analysis between patients on opposite ends of the distribution could reveal prognostic factors or pharmacologic targets, of note would be differences in innate immunity and cellular adhesion.

One issue that is not addressed in the biobanking/retrospective chart review is how to categorize the degree of obstruction. Intraoperative notes may specify that there is no flow or that flow is sluggish upon testing, but this may or may not map to the degree of physical obstruction. For shunts used in our own \textit{ex vivo} experiments, we address this issue by recording the degree of flow volume transport with a buffered solution column before further analysis. Another metric which we want to improve is in how we track if the proximal catheter is touching choroid plexus versus ventricular wall. This will be accomplished by switching from using intraoperative notes to using preoperative imaging where available.

Another limitation of our workflow is that we have not been tracking the total number of hydrocephalus procedures across the multiple centers and thus cannot speak to overall collection rate. There are two major hurdles for a center in obtaining a 100% collection rate. The first is working with surgeons to adopt a new research protocol and collect failed shunts. The next is timely communication to the research team so that consent can be obtained before the family leaves, unless phone consent is approved. There is another minor factor which could affect collection rates and contribute to unintentional selection bias: shunts that are clinically found to be obstructed, or otherwise have failed, but are adherent to underlying tissue and are left in the patient. In our experience, this represents a small number of proximal catheters. Moreover, we defer to clinical judgement and see this as a non-modifiable factor until further advances in catheter material decrease rates of tissue adherence.

The biobank allows for easy investigation into the prevalence of different etiologies and reasons for failure. As it stands, our bank shows a lower prevalence of hydrocephalus due to brain tumors than
The prevalence across the various causes of failure was similar to previously reported values.\textsuperscript{13} Our study shows a persistence of intraventricular hemorrhage of prematurity as the leading cause of hydrocephalus, despite recent reductions in the rates of IVH\textsuperscript{17,18}. The most common etiology at all centers was post-hemorrhagic hydrocephalus.

Our approach of thoroughly cataloguing the patient’s surgical history relevant to hydrocephalus serves as a major advantage to prior collections of failed shunts because it allows for the assessment of the long-term impacts of clinical decision making. Moreover, by collecting failed shunt samples longitudinally, we have several patients for whom multiple samples are banked. This will allow for intra-patient comparisons during translational studies. By having a multicenter design, we are increasing the generalizability of future studies and allowing for comparisons between centers. This will not only help centers institute quality improvement projects but could also be an area of future research if one center is routinely outperforming others.

**Conclusion**

We have created a biobank for samples from failed shunt systems in patients with hydrocephalus for which there is a corresponding database with clinical variables. Currently 6 centers are participating; however, only 4 were presented in this paper due to the limited number of samples from 2 newer centers. Among the 4 centers, there were significant differences in patient age and the number of revisions prior to enrollment in our study; however, the mean interval between replacement of ventricular catheters did not vary significantly. We are still recruiting more centers to contribute failed shunts with their corresponding clinical data. We invite collaboration to utilize this resource, ask new scientific questions, and advance translational efforts.

**Abbreviations**

WSU
Wayne State University
CSF
cerebrospinal fluid
PFA
paraformaldehyde
CNS
central nervous system
IVH
intraventricular hemorrhage
VAS
ventriculoartial shunt
VPS
ventriculoperitoneal shunt
ETV
endoscopic third ventriculostomy
NIH
National institutes of health
IRB
institutional review board
EVD
external ventricular drain
ICP
intracranial pressure
REDCap
Research Electronic Data Capture
MTA
material transfer agreement
WUSM
Washington University of St. Louis, School of Medicine
TEX
Texas Children's Hospital, Baylor College of Medicine
RC
Riley Children's Hospital, Indiana University Health
ALA
Children's Hospital of Alabama at University of Alabama Birmingham
JHU
John's Hopkins Medicine
SD
Standard deviation

Declarations

Ethics Approval: Wayne state University IRB #070915MP2E has approved our study design, our consent form, and our role as coordinating center. All participating centers maintain approval with their own ethics body/IRB for the study and consent form. Informed consent has been obtained for all specimens described in this manuscript.

Consent for Publication: Not applicable.

Availability of data and materials: The datasets analyzed during the current study are not publicly available due to privacy concerns surrounding HIPPA but are available from the corresponding author on reasonable request.

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PZ: Conceptualization, Investigation, Project administration, and Writing—review & editing

PH: Conceptualization, Investigation, and Writing—review & editing

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Figures

New Center Enrollment

Request to be enrolled

Receive study proposal from WSU

Submit proposal to local ethics board

Submit MTAs with WSU and local center

Clinical data MTA

Specimen MTA

Data use agreement

WSU files new center amendment with its IRB

Figure 1

Enrollment Flowchart. Center recruitment is ongoing, as such any centers wishing to contribute or collaborate are encouraged to contact the Harris lab. Thereafter, WSU will send a template study protocol for amendment and submission to the local ethics board. Once the submission to the local ethics committee is approved the requisite MTAs are submitted at both centers. Afterwards, WSU will amend its protocol to include the new center. After which, WSU will remotely train staff at the new center. Only then
can patient enrollment begin. The 'W' badge is next to steps where WSU takes action, and the 'NC' badge is next to steps where the new center takes action.

**Figure 2**

Hydrocephalus History. a The hydrocephalus etiologies of patients enrolled in the study across all centers are shown as percentages. The top 5 causes; post-hemorrhage of prematurity, myelomeningocele, aqueductal-stenosis, brain tumors, and congenital CNS malformations, make up more than 75% of all patients. b The causes for removal of banked hardware across all centers are shown as percentages. Common reasons listed as ‘Other’ include pressure sores and changing from a reservoir to a VPS. Some samples removed for multiple reasons clinically demonstrated proximal catheter obstruction, in total 45.2% of samples had clinically evident proximal obstructions. c and d Box and whisker plots demonstrating the interquartile ranges overlaid on the raw data and respectively show the number of revisions and the number of ventricular obstructions prior to enrollment stratified by center. c The mean number of prior revisions are as follows: WSU 8.53, WUSM 1.99, TEX 1.65, and RC 1.64. d The mean number of prior ventricular obstructions are as follows: WSU 2.73, WUSM 0.15, TEX 1.03, and RC 0.36. **** p-value<0.0001 by Kruskal-Wallis H test. *denotes numeric outliers more than 3 SDs away from the mean for each center.
Figure 3

Ventricular Catheter Implant Duration. A Box and whisker plots demonstrating the interquartile range for each center overlaid on the raw data for length of time, in months, that each ventricular catheter was implanted before requiring removal, the distributions are not significantly different from one another. *denotes numeric outliers more than 3 SDs away from the mean for each center.