2019 Bobby Jones CSF Research Colloquium Proceedings

Advances and Challenges in Chiari Malformation, Syringomyelia and Related Disorders

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Contents

Allison Ashley-Koch, PhD is a Professor in the Department of Medicine at Duke University Medical Center. She received her Ph.D. in genetics and molecular biology from Emory University. Dr. Ashley-Koch is a genetic epidemiologist whose primary goal is the identification of genes that contribute to human genetic disorders, including gene-gene and gene-environment interactions. She has a particular interest in the genetics of Chiari Type I Malformations, with and without Syringomyelia. She and her colleagues at Duke are working to identify genetic risk factors for Chiari using a variety of methods, including whole genome genetic analysis, sequencing of candidate genes, and gene expression studies. She is particularly interested in using radiologic and clinical features to distinguish subtypes and clinical heterogeneity in these malformations.

Alexandre Casagrande Canheu, MD was born in the state of São Paulo, and graduated in 2000 from the UNESP Faculty of Medicine of Botucatu-SP. He was a monitor of Neuroanatomy and Neurological Semiology for 4 years, including publishing papers in internationally indexed journals. From 2001 to 2005, he practiced with one of the most renowned Neurosurgery services in Brazil, at the Faculty of Medicine of USP Ribeirão Preto-SP.

His first work in Europe was in 2008 at the European Congress of Pediatric Neurosurgery, held in Montreux, Switzerland where he presented a rare case of spinal malformation operated on a child in the first months of work in Cianorte. In 2009 he attended the Policlinico Agostino Gemelli of the Catholic University of Rome, Italy, in a scientific exchange. In 2010, he specialized in Medical Management at Fundação Getúlio Vargas (FGV-SP). In 2011, he traveled briefly to Europe, where he remained for five weeks as a Clinical Fellow in the Charité-Universitätsmedizin Pediatric Neurosurgery Department in Berlin, Germany, actively participating in surgery. In 2012, he returned to Europe, this time as an affiliate member elected by the European Society for Pediatric Neurosurgery. He presented 3 more works of his own at the European Congress of Pediatric Neurosurgery, held in Amsterdam, Netherlands. In 2014, he presented another paper at the European Congress in Rome, Italy, and in 2015, he received the title of International Fellow of the American Association of Neurological Surgeons, a distinction imparted on few Brazilian neurosurgeons.

In 2016, he was again at the European Congress in Paris, France, presenting two more cases based on experience gained in recent years in Londrina. In 2018, he traveled to Bonn, Germany to present his latest results in surgical intervention for brain hemorrhage in extremely premature infants.

Since 2017, he has worked at the London Spasticity Clinic, headquartered at the Pro-Kids Institute, together with Dr. Alessandro G. Melanda, Dr. Marcos Antonio Dias, and Dr. Kleber

Kawagoe. The clinic has focused on several cases of cerebral palsy, leading to the improvement of the quality of life of several children from Londrina and region— especially with the introduction of Selective Dorsal Rhizotomy.

In 2019, Dr. Canheu is now charged with chairing the Consensus SBNPed: Craniocervical Junction, which was held on 2 and 3 August in London, UK. At this event, the biggest national names of pediatric neurosurgery, skull base and spine are expected and a guidebook will be designed on the best practices for each case, especially focused on Chiari I malformation.

John D. Heiss, MD is Head, Clinical Unit, in the Surgical Neurology Branch, NINDS, at the National Institutes of Health in Bethesda, Maryland and Clinical Professor of Neurosurgery, George Washington University, Washington, DC. He is the Principal Investigator of clinical research protocols that examine the pathophysiology of syringomyelia and the genetics of Chiari I malformation. He is Vice-Chair of the NINDS Institutional Review Board and former Chairman of the Surgical Administrative Committee.

An expert in surgery for brain tumors, syringomyelia, and epilepsy, Dr. Heiss has lectured extensively on various topics in neuroscience and neurosurgery, and has published dozens of original research papers, review articles, and abstracts based on his research. He has served on grant review panels for the National Cancer Institute. Dr. Heiss is board certified in neurological surgery by the American Board of Neurological Surgery.

Fraser C. Henderson, Sr., MD was foreman on a cattle station in the Outback of Australia before receiving his bachelor's and Medical degree at the University of Virginia, Charlottesville VA. He served with the Multi-National Peace Keeping Force in Beirut, earning the Navy Commendation Medal for preparedness of and treatment of mass casualties following the terrorist bombing attack in Beirut, Lebanon, in October 1983. After completing his residency under Phanor Perot at the Medical University of South Carolina, he returned to complete his active duty obligation at the National Naval Medical Center, Bethesda, MD, as Director of Spine Surgery. He was Brigade Neurosurgeon for the 4th Marine Expeditionary Brigade in Desert Shield and Desert Storm during the 1st Gulf War. He then completed a fellowship in craniospinal surgery under Professor Alan Crockard at The National Hospital for Neurology and Neurosurgery, Queen Square, London.

Finishing his tour with the US Navy, Commander Henderson joined Georgetown University, in Washington D.C. as Director of Neurosurgery of the Spine and Cranio-cervical Junction. He was Co-Director of the Lombardi Neuro-Oncology Division, Co-Director of the CyberKnife Radiosurgery Center, and Medical Director of the Neuroscience Nursing Units. He

was Professor of Neurosurgery and Radiology at Georgetown University, where he was active in advancing CyberKnife radiosurgery for treatment of chordoma and other complex spinal tumors. He developed three inventions relating to spinal radiosurgery and spinal cancer, including the TPS® –Telescopic Plate Spacer- a vertebral replacement device for metastatic disease and was Principal Investigator in the translational development of a radio-sensitizing drug, and a drug to block the malignant invasiveness of Glioblastoma Multiforme.

Dr. Henderson entered private practice in Bethesda, Maryland, as Director of Neurosurgery at Doctors Hospital and Director of the Chiari Center of Excellence, where he is focused on the development of the understanding and treatment of deformity-induced injury to the brainstem and spinal cord in Chiari Malformation and Ehlers Danlos Syndrome. He is inventor of 13 devices and concepts relating to disorders of the brainstem and spinal cord, and has published over 90 peer reviewed articles and book chapters, and given over 180 invited lectures with a focus on craniocervical disorders, Chiari malformation, cancer, radiosurgery and unusual problems of the spine.

Eric M. Jackson, MD is an Associate Professor of Neurosurgery at the Johns Hopkins University School of Medicine. He graduated from Harvard College and received his medical degree from the University of Michigan Medical School. He completed his Neurosurgery residency at the University of Pennsylvania, followed by a fellowship in Pediatric Neurosurgery at Children's Hospital Boston. He was a Pediatric Neurosurgeon at Nationwide Children's Hospital prior to accepting his current position in the Department of Neurosurgery at Johns Hopkins.

Clinically, he sees patients with a broad range of diagnoses including hydrocephalus, Chiari malformation, craniosynostosis, brain and spinal cord tumors, spinal dysraphism.

He is the Principal Investigator for Johns Hopkins for many multi-institutional research consortia including the Hydrocephalus Clinical Research Network, the Park-Reeves Syringomyelia Research Consortium, and the Advancing Treatment for Pediatric Craniopharyngioma Consortium.

He is a member of the Executive and Scientific Committees of the Children's Brain Tumor Tissue Consortium. He is currently a Member-At-Large of the Executive Committee of the AANS/CNS Joint Section on Pediatric Neurosurgery.

David D. Limbrick, MD, PhD, is a pediatric neurosurgeon at St. Louis Children's Hospital, Washington University in St. Louis. Dr. Limbrick graduated with a B.S. (Biology) from the College of William and Mary as well as an M.S. (Physiology), Ph.D. (Pharmacology) and M.D. from the Medical College of Virginia. His graduate research training was in cellular neurophysiology in the laboratory of Dr. Robert DeLorenzo and in molecular biology in Joshua Rubin's lab at Washington University.

Dr. Limbrick's clinical interests include epilepsy surgery, hydrocephalus and surgery of the craniovertebral junction. His research has focused on cerebrospinal fluid physiology in the setting of developmental brain injuries and syringomyelia. He is currently an Assistant Professor of Neurological Surgery and Pediatrics.

Catherine A. Loughin, DVM grew up in a small town west of Cleveland, Ohio. Her interest in animals began at the age of 4 when her father brought her to their cousin's veterinary clinic. Her cousin was proficient in canine and equine surgery, and his influence guided her career into veterinary surgery. Dr. Loughin obtained her bachelor's degree in biology from the University of Michigan, and doctor of veterinary medicine from Michigan State. Dr. Loughin was a general practitioner for 2 years at Animal Medical Hospital in Charlotte, NC. She then accepted a 1 year general internship at Long Island Veterinary Specialists. That one year progressed into a second year as a surgical intern, and then 3 more years for a surgical residency and she is now a staff surgeon.

Dr. Loughin has published over 20 research papers, several book chapters, and has been an invited lecturer locally, nationally and internationally. She is one of the founding members of the Canine Chiari Institute at Long Island Veterinary Specialists, and she is the director of education and research. A member of the Board of Directors of the Bobby Jones Chiari & Syringomyelia Foundation as of 2019, she is also the treasurer. Dr. Loughin's surgical interests are neurosurgery, orthopedic, and reconstructive surgery.

John J. Oró, MD earned his medical degree and completed surgical internship at the University of Texas Medical Branch at Galveston. He then obtained neurosurgical training at the University of Missouri Health Sciences Center in Columbia, MO. He was in academic practice for 21 years at the University of Missouri Health Sciences Center in Columbia. For 14 of those years, he served as Chief of the Division of Neurosurgery and Director of the Neurological Surgery Training Program.

Dr. Oró was recipient of multiple teaching awards at MU. He founded the MU Neurosurgical Research Laboratory and performed pioneering work on motor cortex stimulation. He also contributed to the early studies on magnetic stimulation of the motor cortex in humans. Dr. Oró has published more than 70 research articles and book chapters.

To enhance educational opportunities, he created the Division of Neurosurgery Visiting Scholars Program for international neurosurgeons and served as Co-Director of the MU Spine Fellowship Program. Dr. Oró also served on the Board of Directors of the American Association of Neurological Surgeons.

Dr. Oró has a long interest in the treatment of the adult Chiari malformation and syringomyelia. At University of Missouri, he and Diane Muller, ND, RN, FNP-BC, established The Chiari Clinic. Moving to Denver, Colorado in 2005, Dr. Oró became Director of Neurosurgery at The Medical Center of Aurora and The Chiari Care Center. Dr. Oró has presented his work internationally and, together with Diane Muller has written a number of seminal papers on the disorder. Recently, he has narrowed his practice to the evaluation and treatment of persons with the Chiari I malformation and in 2017, together with Kimberly Sexton, MSN, RN, FNP-BC, established the Colorado Chiari Institute at The Medical Center of Aurora.

Adnan I. Qureshi, MD is recognized as an international leader in stroke and neuro-endovascular research and acute stroke management by physicians from multiple disciplines. He has written over 300 scientific publications in prestigious journals including the New England Journal of Medicine, Lancet, Archives of Internal Medicine, Critical Care Medicine, Neurology, Stroke, and Circulation. He has made over 700 presentations in various national and international meetings. He has served as an invited speaker at numerous national and international forums. He has also been invited as visiting professor to universities in the United States and abroad.

He serves on editorial boards for several peer-review journals and is Editor-in-Chief for "International Journal of Biomedical Sciences" and "Journal of Vascular and Interventional Neurology" and Associate Editor of the "Journal of Neuroimaging". He was the section editor for a supplement of Journal of Endovascular Therapy. He was also the editor of the "Atlas of

Interventional Neurology" published by Demos in 2008 and "Textbook of Interventional Neurology" to be published by Cambridge. He is currently the principal investigator of Antihypertensive Treatment of Cerebral Hemorrhage-II, a large multicenter international randomized trial that will recruit 1300 patients with intracerebral hemorrhage.

Most recently, he laid the foundation of the Zeenat Qureshi Stroke Research Center. Since its inauguration, the center has led the way in cutting edge research in epidemiology, clinical trials, and basic research pertaining to cerebrovascular diseases. Several investigators in the center receive funding through National Institutes of Health, American Heart Association, and Armed Forces Research Initiatives. Dr. Qureshi has made a significant effort towards developing treatments for both intracerebral hemorrhage and ischemic stroke. His pioneering work on the use of hypertonic saline, third generation thrombolytics, platelet glycoprotein IIB/IIIA inhibitors, and antihypertensive treatments has found rapid clinical applications

Dr. Qureshi has mentored several fellows and medical students. He has trained several clinical fellows in cerebrovascular diseases and endovascular procedures. Several of his students and fellows have won national awards for research performed under his direct supervision. He continues to serve as course director for various educational seminars at a regional and national level.

Courtney Rousse Sparks earned her Bachelor of Science degree in Biochemistry and Molecular Biology from the University of Richmond while attending on a women's golf scholarship. During her undergraduate years, she developed a passion for neuroscience and translational research while working in a research laboratory focused on the effects of pregnancy on learning and memory using a rodent model.

Currently, Courtney is a candidate in the DVM/PhD dual degree program at North Carolina State University's College of Veterinary Medicine under the direction of Dr. Natasha Olby, a veterinary neurologist and neurosurgeon. Courtney's dissertation work is centered around characterizing the canine Chiari model and investigating the complex genetic inheritance of this condition in Cavalier King Charles spaniels.

Overall, her research interests are focused on the genetic basis of complex diseases and neuropathic pain with the goal of using the canine model as a translational approach to deepening our understanding of inheritance and treatment options for neurodegenerative diseases in humans. Her veterinary medicine interests include neurology, radiology, anesthesiology, and pain management. She has co-authored 5 publications and was awarded the Ruth L. Kirschstein National Research Service Award Individual F30 Fellowship in 2018.

Kristen Yeom, MD obtained her medical degree from University of Michigan. She completed her radiology residency training at UCLA and neuroradiology fellowship at Stanford University, where she currently practices. She is board certified in Diagnostic Radiology and also holds Certificate of Added Qualification in Neuroradiology.

Her primary interest is pediatric neurological diseases. Her research also includes the use of advanced MRI techniques to improve detection, surgical navigation, as well as image-based monitoring of pediatric brain tumors and associated therapeutic sequelae.

Introduction

ULRICH BATZDORF, M.D.

The Bobby Jones Chiari Syringomyelia Foundation has once again brought together a group of investigators who share the goal of improving our understanding and care of patients with Chiari anomalies and syringomyelia.

It is encouraging that the contributions to this seminar reflect not only problems related to the clinical care of the human and canine populations, but also deal with genetics, imaging and the increasing appreciation of co-morbidities. Re-examining the value of long established concepts and techniques with modern objective measures is another great advance. There can be no question that we are all beneficiaries from this interdisciplinary approach, which ultimately benefits patients with these disorders.

We all owe our thanks to the Bobby Jones Chiari & Syringomyelia Foundation and to Dorothy Poppe and her excellent staff for bringing this group of dedicated people together and organizing this meeting.

1.

Brazilian Consensus for Chiari I: Results and Flow Chart

ALEXANDRE CASAGRANDE CANHEU, M.D.

Disclaimer

The preferred language of Dr. Canheu is *not* English. This presentation was given in English as an oral presentation and then edited for written clarity. These factors may have impacted the meaning of certain words and phrases which may have been lost in translation to English, or to the written word. Specific questions about the content of this presentation can be directed to Bobby Jones Chiari & Syringomyelia Foundation or Dr. Canheu.

Introduction

Thank you so much. We brought together Brazilian neurosurgeons in an attempt to come to consensus on Chiari malformation, as there seem to be significant differences in clinical practice for this condition. We hosted this meeting in Londrina which is located in Southern Brazil in the Paraná State. The city was founded by an Englishman who named it "little London" just because it has a morning fog very similar to the city of London, England.

We had a two-day program for this consensus program, focusing on all the main issues related to the definition of Chiari malformation. The talks were really productive and our rooms remained quite full. Dr. Brandon Rocque kindly spent a lot of time video conferencing with us during the meeting.

Background

The consensus was necessary because there were several misunderstandings that were occurring in the treatment of pediatric Chiari I. Additionally, we felt that it was important to face the current lack of Brazilian guidelines for the treatment of Chiari I. At the same time, we wanted to have objective measures of knowledge and attitudes regarding the diagnosis and treatment of Chiari I malformation. Ideally, we wanted to test if this meeting was an effective tool to change any misconceptions in a majority of the attendees.

Another important reason that this Brazilian consensus conference was held had to do with litigation. There have been several lawsuits that obligated the Brazilian Public Health System to pay for surgeries that had previously been done at an external, international institute accepting patients from around the world. They have staff that speak multiple languages including Portuguese and as such, some of our patients made their way over there. This clinic developed a new trademarked surgical treatment and has asserted it can resolve all neuroaxis illnesses including Chiari I, syringomyelia, scoliosis, basilar impression, et cetera. The problem is that this has been marketed as a sort of panacea. Our Brazilian colleagues recently published a systematic review analyzing the effect of filum terminale sectioning to treat Chiari I malformation and concluded that this surgical intervention is still experimental, with level 4 evidence.[1]

All of this, therefore, further strengthened our argument that a Brazilian consensus on Chiari malformation would be important.

Determining Definitions and Standard Imaging from the Evidence Base

Our first step in developing consensus was about naming the disease. As recently suggested by Dr. Thompson and Dr. Di Rocco[2,3], we preferred to describe Chiari as a "deformity", rather than as a "malformation" because there are several conditions that can lead to Chiari I and we preferred the term deformity.

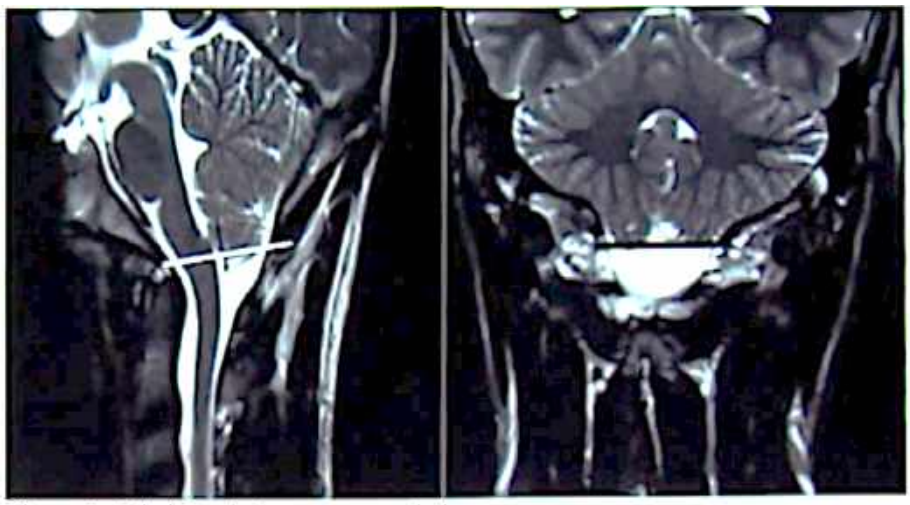

Figure 1. Chiari I sagittal versus coronal view

With respect to the imaging, the usual point is at 5 mm ectopic tonsils at the minimum to diagnose the deformity. As the audience here knows, we used to draw a line between the basion and the opisthion and by this historical definition of Chiari, the tonsils would descend beyond this— McRae's— line. For the purposes of our consensus, we stated that 5 mm below McRae's line would be called a Chiari I deformity (CID).

Dr. Tubbs and his colleagues have done excellent work regarding the coronal view of CID.[2] It is very important to analyze the image not only on the sagittal, but also on the coronal view of the tonsils. As you know, the tonsils are not only midsagittal structures; they may be asymmetrical in the coronal view. **(Figure 1)** Additionally, we need to remember that head flexion and extension may also change the tonsillar position.

When asymptomatic, CID may present with or without syringomyelia. We suggest that in cases without syringomyelia, clinicians should be more conservative, perform a neuroaxis MRI, do consultations and a clinical analysis every 6 months and repeat the cranio-cervical MRI the following year. If the one year MRI is normal, it should be repeated after 2 years. If the two year MRI is normal again, it can be repeated after 3 years. However, in cases of CID with clinically significant syringomyelia, we prefer to perform a posterior fossa decompression.

For the purposes of consensus, CID symptoms were divided into two main groups: minor and major symptoms. Minor symptoms were characterized by non-specific headaches, numbness, paresthesias and dizziness. The major symptoms were described as symptoms related to motor pathways, cranial nerves and central apnea. Major symptoms listed also included: nuchalgia, tussive headaches, decreasing fine motor skills, cerebellar findings, central cord syndrome and progressive scoliosis.

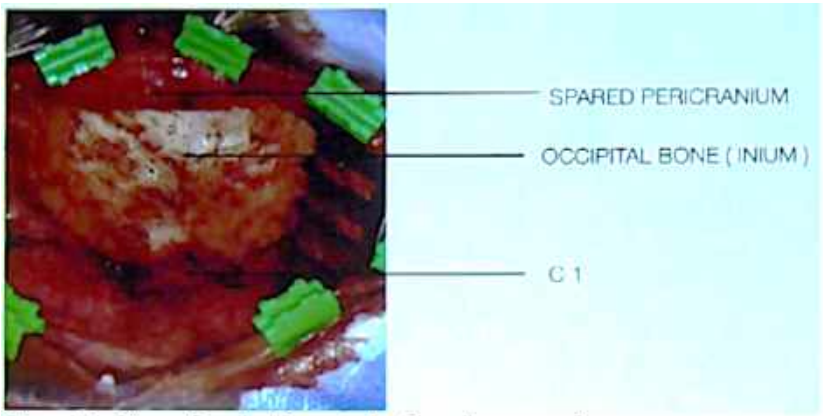

Figure 2a. View of occiput in posterior fossa decompression

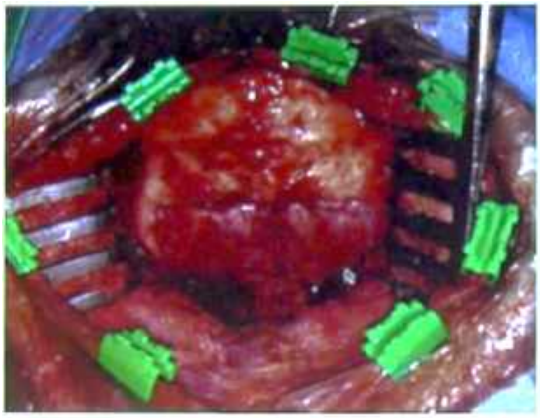

Figure 2b. Posterior fossa decompression (cont.)

Specifically for symptomatic patients, we suggest performing neuroaxis MRI, dynamic studies which may be either CT scan or MRI, and for those who complain of snoring or other sleep disorders, a sleep study. If during the clinical investigation hydrocephalus is discovered as a concomitant finding, we first try endoscopic ventriculostomy (EVT).

For the surgery itself, we prefer prone positioning, being sure to pad points of contact and keeping the shoulders out of the operating field. My personal preference for incision also includes a little extension upwards in order to dissect the pericranium for a dural patch, if necessary.

In **Figure 2a** I would like to draw attention to the spared pericranium, the occipital bone or inium and the position of the posterior arch of C1. The bone removal must be at least 3 cm up above the foramen magnum. **(Figure 2b)** It may not be necessary to go as far lateral as I have done here, but also never forget to remove the posterior arch of C1.

During my surgeries, I also always use an ultrasound probe to check for adequate space in the cisterna magnum after the decompression. A relatively recent paper echoed this concern.[5] We choose to do a duraplasty when it is not possible to expand the cisterna magna.

In a case of additional instability with CID and syringomyelia, we decompress and do a posterior fusion based on the case and the surgeon operating. **Figure 3** shows the MRI of a case such as this, where we can see improvement of the syringomyelia. Importantly, all of the clinical symptoms of the patient improved after the surgery, as well.

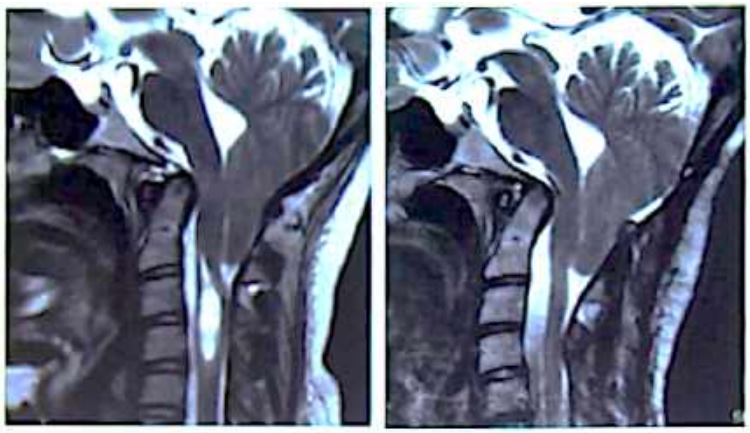

Figure 3. Patient with instability before and 1-year post-op, posterior fossa decompression and fusion

Consensus Flowchart

We developed the flowchart shown in **Figure 4**. Every case of CID should be screened, first, for potential secondary causes including hydrocephalus, craniosynostosis, tethered cord or metabolic causes. If the CID is the primary diagnosis, we follow the flow chart. If we find an asymptomatic patient without syringomyelia, we follow the patient as mentioned before. If we find syringomyelia in an asymptomatic patient, we do a posterior fossa decompression because there is a likelihood for improvement in that syrinx.

At the right side, we see symptomatic patients. As discussed before, we screen with neuroaxis MRI, dynamic CT or MRI and polysomnography specifically in the cases of patients with complaints of snoring or sleep disorder. If we have a child with CID and no syrinx, we do a posterior fossa decompression with intraoperative ultrasound to check the space available in the cisterna magna. Autologous duraplasty is advised.

On the other hand, if there is a syrinx, our protocol suggests doing the posterior fossa decompression with a duraplasty, regardless of the results of the intraoperative ultrasound. After discharge and following a 6 month follow-up in this patient, we recommend revision surgery if symptoms relapse or persist. This surgery would include a revision of the original posterior fossa decompression with duraplasty and tonsillar coagulation to increase space in the posterior fossa.

Finally, if the imaging studies appear to show vertebrobasilar impression (VBI), we recommend posterior fossa decompression and a posterior fusion.

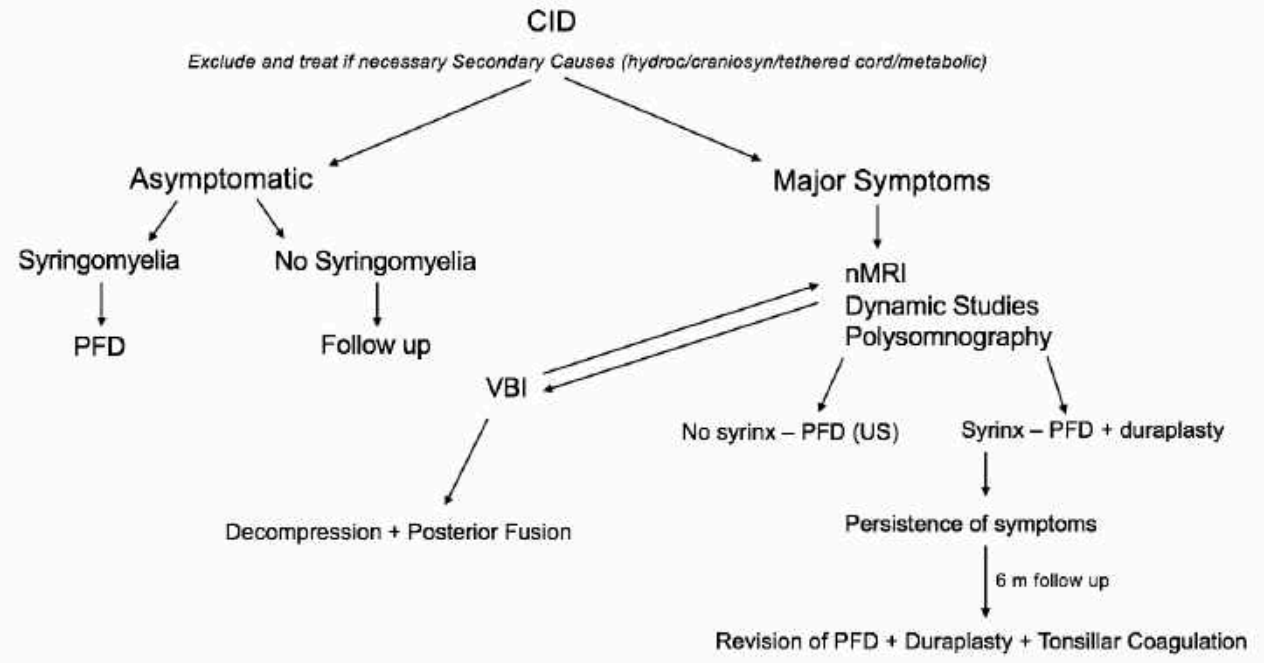

Figure 4. Brazilian consensus flowchart. (Canheu AC, et al. 2020)

Measuring Effectiveness

In addition to developing these consensus recommendations, we also wanted to measure their effectiveness on clinical practice. To that end, we administered the same questionnaire before and after the consensus meeting in an attempt to measure how the meeting may impact attitudes about the diagnosis and treatment of CID.[6] At the opening of the consensus we sent 27 questions to the mobiles of all attendees using the SurveyMonkey application. Thirty-four answers were recorded. At the closing of the consensus, the same questions were sent out and we received 33 answers in response. The results of both surveys were compared using Cochran's Q test and the McNemar test. Statistical analyses were performed using SPSS v.24, IBM Corp.

The first question wherein we saw a statistical difference in responses was related to length of follow-up in incidentally diagnosed, asymptomatic infants. Before the meeting, a little more than half of the respondents would follow that child for ten years. After the meeting, 27% reported that they would follow for three years, 21% would follow for five years and only 30% then reported that they would follow these patients for ten years. ($p < 0.01$)

Question number four asked which of the following late symptom appeared with the most frequency: hydrocephalus, spasticity, nocturnal respiratory symptoms, scoliosis and muscular atrophy. Before the meeting, 47% of the respondents chose scoliosis. By the end of the consensus meeting, almost seventy percent chose scoliosis. ($p < 0.01$)

The next question that was of statistical significance pertained to Chiari 0 and its clinical legitimacy. Before the meeting, eight respondents claimed that it did not. By the end of the consensus meeting, we were able to convince the majority that Chiari 0 does indeed exist— 93.9% of respondents agreed that Chiari 0 was indeed a real clinical finding. ($p < 0.03$) Two respondents, however, still did not believe that Chiari 0 was a valid clinical diagnosis.

The last question where we found a statistical difference was question 19: "In your opinion, related to Chiari, should every case be screened for instability?" Before the meeting 58.8% of the respondents agreed that every case should be screened. After the meeting, 64% of respondents disagreed and did not believe that every case of CID should be screened for instability. This was highly significant, with a *p*-value of 0.008.

Conclusion

We were able to outline the previous flowchart for the management of this complex pathology based upon current standards of all international societies of pediatric neurosurgery. Chiari I deformity is being critically analyzed and studied and consensus debates continue to go forward with the same energy in many countries in Europe, Asia and the Americas. These consensus and educational initiatives should not be overlooked. Future consensus meetings on this matter and on other controversial topics are being planned. There is great anticipation for the ever-growing and relevant scientific evidence base, to which we all hope to contribute. Specifically for Brazil, we will be hosting our next task force meeting in August 2020 Aracaju-Sergipe of northeastern Brazil. We will be discussing myelomeningocele in fetal neurosurgery. We will be able to enjoy some delicious crabs and we hope to see you there. Thanks for your attention.

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2.

Orthostatic Intolerance and Update on Epidural Interventions

ADNAN I. QURESHI, M.D.

Introduction

Thank you very much for having me here today. I am Adnan Qureshi and I am from Columbia, Missouri. Today, I am going to be discussing our work on epidural postural intolerance and talk a little bit about epidural interventions.

What is upright posture intolerance? In fact, it is the inability to stand upright without any difficulty. Now we all know of upright posture intolerance as being a cardinal feature of intracranial hypertension in acquired Chiari malformation.[1] However, it can be seen in many conditions. It can be seen in postural hypotension[2] and postural tachycardia.[3,4] It can be seen in various cerebellar and spinal ataxias[5,6,7] and vertebrobasilar arterial ischemia[8] and vestibular dysfunction.[9] Simply, it can also be seen with advancing age[10], since the muscular reflexes are not as robust.

My interest in upright postural intolerance did not start in the clinic— it actually started in the zoo! I was visiting the zoo, and I was actually looking at the giraffe, and I was just fascinated about how the giraffe can move its neck and head several feet and distances without having any orthostatic symptoms. So, I did a little more research about how a giraffe can adapt to such postural changes. It appeared that the giraffe actually has veins that drain from the brain, and these veins have valves or, at least, are very high resistance vessels to allow blood to leave the brain in a very controlled fashion.[11] The question then becomes: do similar mechanisms also exist in human beings?

Role of Cerebral Drainage in Upright Posture

To address that question, we started with what is called an *upright cerebral angiography*. We all know of cerebral angiography being performed in a supine position. But you can also tilt the table into a certain position to a specific degree, and then repeat the imaging at that specific degree to identify any change in venous drainage in normal patients. The left image illustrates what the cerebral veins look like when the patient is supine **(Fig. 1, A)**. You can see that there is a prominent contribution of the internal jugular veins. Now, if you turn the patient into an upright position (**Fig. 1, B**), you will notice that the role of the internal jugular vein diminishes considerably and there is far more of a role that is played by the paravertebral or the ancillary veins in terms of drainage of

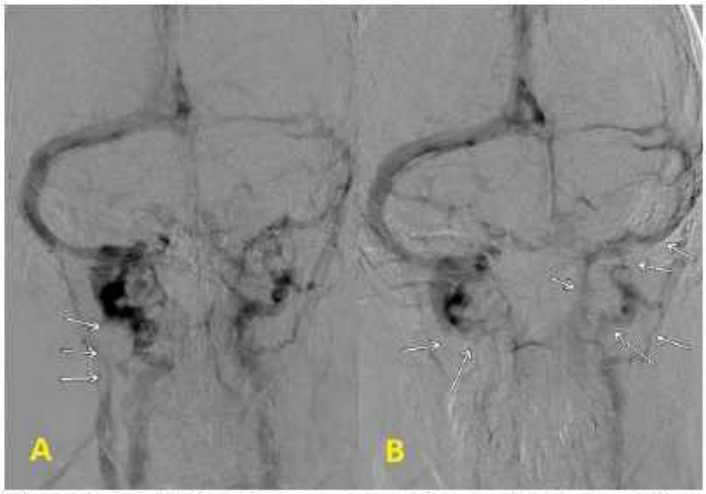

Figure 1. Cerebral angiogram. Left, patient supine. Right, patient upright.

blood flow from the brain.[12] The point of this is that the internal jugular veins and their patency are what we usually rely on to determine whether there is truly an effective cerebral venous system drainage. But, in fact, in the upright position, that may not even matter much.

On top of this, there is so much variance. For many people, the internal jugular vein is not the main drainage system; they have supplementary venous systems. In fact, in almost half of the patients we see, there are supplemental veins that drain blood from the brain in addition to the internal jugular vein. These supplemental veins are smaller, have higher resistance and perhaps are more amenable to compression from the external muscles.[13] So, there is clearly a large variation in the cerebral venous system and a postural related role that may play an important role in upright postural intolerance. This is all to suggest that perhaps the next series of interventions we develop may be neither epidural nor surgical, but rather trans-venous interventions.

Quantification of Upright Posture Intolerance

Of course, we had been doing all of these epidural interventions and the patients always reported an improvement in their ability to tolerate an upright posture. But we never really had a measure where we could, at least to some extent, quantitatively understand the type and timing of the patient response to treatment. So, we developed a questionnaire **(Table 1)**.[14] Specifically, we chose a self-administered questionnaire, because perhaps the patients would serve as the best judge of whether they do or do not have tolerance to an upright position. The questionnaire seeks to address and quantify various components of upright posture intolerance. And obviously, ease-of-use and repeated feedback from the patient about whether the items about which we are inquiring are really pertinent was also an important feature in the development of such a questionnaire.

Question	Responses
How long can you stand straight without any support?	1. Cannot stand straight without any support 2. Less than 5 minutes 3. 5-29 minutes 4. 30 minutes or greater
Do you feel any sense of sickness (headache, nausea, dizziness, lightheadedness, etc.) when you sit or lie down after standing straight with or without support?	1. Not at all 2. Less than 5 minutes 3. 5-29 minutes 4. 30 minutes or greater
How long do you have to wait before you are comfortable standing again after you have stood straight with or without support?	1. Not at all 2. Less than 5 minutes 3. 5-29 minutes 4. 30 minutes or greater
How effectively and fast can you get up from sitting or being in a lying position to stand straight without any support?	1. Can stand up easily without interruption/support 2. Have to stand up from sitting or lying position with interruption (slow) or in two steps or more 3. Must hold on to temporary support (less than 5 minutes) to stand up from sitting or lying position
Rate your ability to perform activities such as household chores, office work, writing, reading, eating, toilet activities while you are standing without any support.	0 (Worst) 60 10 70 20 80 30 90 40 100 (Best) 50

Table 1. *Questionnaire*. Quantifying upright posture intolerance.

We identified four items for the questionnaire:

1. How long can you stand straight without any support?
2. Do you feel any sense of sickness (headache, nausea, dizziness, lightheadedness, etc.) when you sit or lie down after standing straight with or without support?
3. How long do you have to wait before you are comfortable standing again after you have stood straight with or without support?
4. How effectively and fast can you get up from sitting, or being in a lying position, to stand straight without any support?

We specifically included the second question because patients were frequently reporting a "hangover syndrome." We included the third question because of the potential period of normalization and confidence-development required for standing. The last question was included because many patients reported being in need of support before transitioning from a supine to upright position. Obviously, we had to stratify our quantitative values such that the patient could report increased or decreased symptoms following treatment. For the first three questions the quantitative measure is easier. The strata for the first few questions were set in terms of an increasing amount of time: not at all, less than 5 minutes, 5-29 minutes, and 30 minutes or greater. The last question, however, was stratified in such a way that patients would report the relative difficulty and speed with which they were able to move from a supine to upright position. Patients may be able to do so with or without any support, or even in steps.

Recently, there has been a greater emphasis on the use of the standard vertical visual analog scale. We included this as a component in our questionnaire. The patient is asked to rank their ability to perform everyday activities (such as household chores, office work, writing, reading, eating, toilet activities) while in a standing position on a scale from 0 to 100, where 0 represents that nothing can be done at a standing position and 100 represents that everything can be done in the upright position.

Initial Testing

The questionnaire was tested prospectively for patients who came in with intracranial hypotension in whom we were performing a lumbar epidural blood patch. Questionnaires were administered at: baseline, immediately after the procedure, and at 1 month follow-up. The two questions that had the most consistent response in terms of improvement were related to length of time being able to stand without support and rating of ability to perform everyday activities. All patients consistently demonstrated improvement in those particular scales.

For the other three questions, the responses were mixed. Perhaps there is a greater level of subjectivity in the interpretation of these questions. The other interesting thing was with some of these patients that had pre- and post-MRIs. Of the patients reporting an improvement in symptoms after the procedure, there were no concurrent radiological changes. Apparently, then, there could be clinical improvement of symptoms in intracranial hypotension without clear radiological change.

Epidural Intervention Effects in Patients Without Intracranial Hypotension

What is the role of epidural interventions in Chiari Malformation, unrelated to intracranial hypotension? This is a patient with Marfan Syndrome who also had a Chiari malformation. The patient came in for an epidural intervention, but hydrocephalus and a perineural cyst were also present, which are not typical symptoms of intracranial hypotension. So, the question became whether or not an epidural intervention would even help the patient. Certainly, the last thing we would want is to make the patient's symptoms worse by inputting blood into the epidural space, effectively limiting the space for CSF flow.

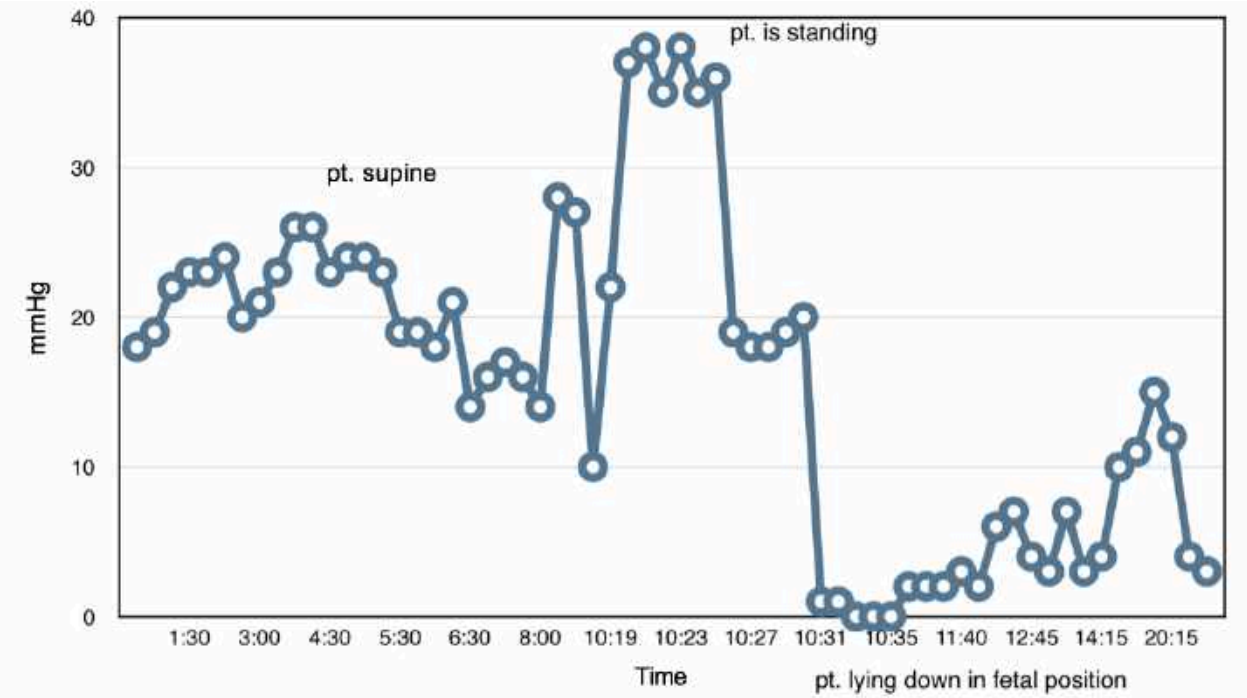

Figure 2. Cerebrospinal fluid pressure monitoring via lumbar catheter (mmHg) in various postures.

We decided to do intracranial pressure monitoring before proceeding with an epidural intervention. **Figure 2** shows the patient's CSF pressure measurements in various postures measured via a lumbar catheter. You may notice that, in general, this patient actually has high CSF pressure during the recording and the CSF pressure increased dramatically when the patient stood up. Symptomatically, the best position was when the patient was in a fetal position, within the head positioned below the body. There is a clear dramatic decrease in the CSF pressure in that particular position, concurrent with symptomatic relief.

So, we can clearly identify a syndrome— but how do we explain this? Frankly, I don't really have the clearest explanation. All I can really offer is a hypothesis that perhaps the tonsillar descent in certain Chiari malformation patients may be postural dependent. While the patients are in a supine posture, there may be only some tonsillar descent but as soon as they move into an upright position, there may be a marked tonsillar descent, significantly blocking CSF flow. This leads to a dramatic change in intracranial CSF pressure. Then as the patient moves into the fetal position, some of this tonsillar descent is relieved by this position and the intracranial pressure

dramatically reduces or normalizes. It almost transforms an intracranial hypotension-like syndrome. We hypothesized that if we could relieve this postural dependent tonsillar descent, perhaps the patient's syndrome can actually be improved.

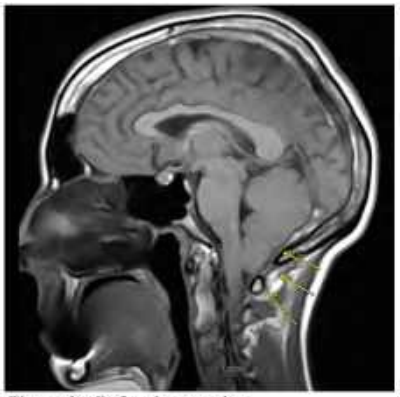

Figure 3a. Before intervention

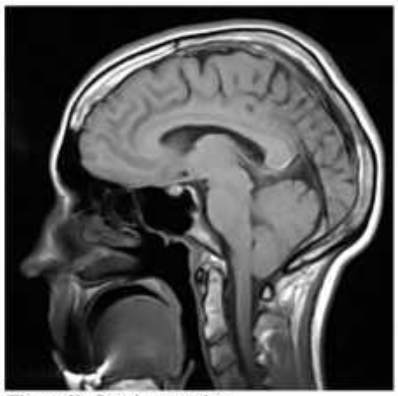

Figure 3b. Post intervention

To test this theory, we did a blood patch, also injecting fibrin sealant for sustainability. We decided to inject this into the caudal epidural space and go to the sacral hiatus, with the concept that we could get more of the blood and the fibrin sealant there. In **Figure 3a**, you can see a marked tonsillar descent before the procedure. Looking at the MRI after the procedure, there is clear improvement in the tonsillar descent. **(Fig. 3b)** There is also clinical improvement of patient symptoms. However, in the setting of intracranial hypotension, the CSF leak is temporary or transient but in the setting of Chiari malformation, the causal defect remains. The question for these patients then becomes: how long will the effect of an epidural injection last?

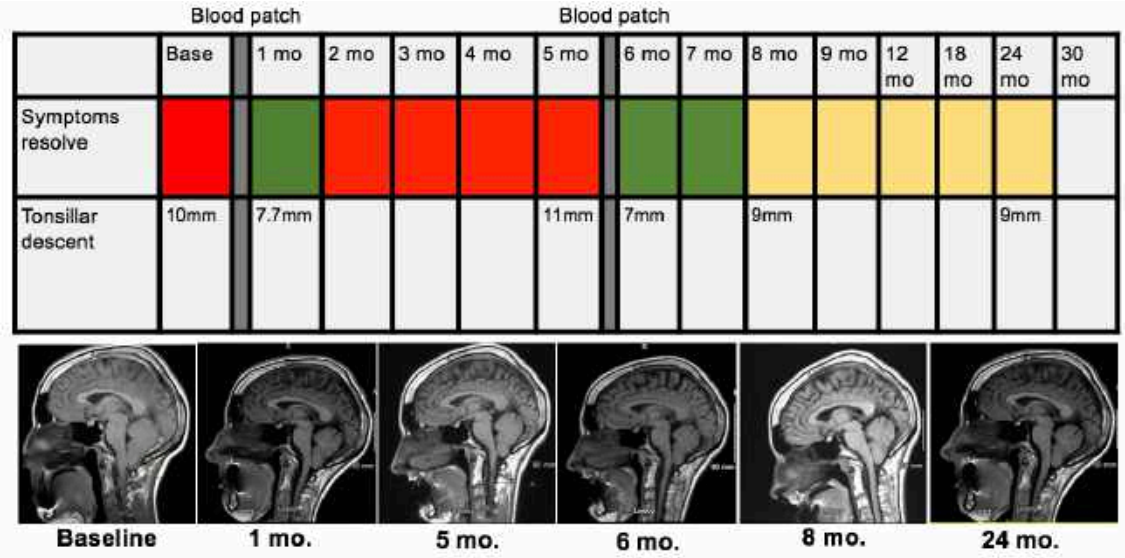

Figure 4. Clinical and radiological effects of epidural blood patch injection for Chiari malformation in patient with Marfan syndrome. Red indicates persistent/worst symptoms, yellow indicates partial relief of symptoms, and green indicates least bothersome symptoms.

To learn more, we followed this patient serially. **(Figure 4)** We had concurrent MRIs available, as well, which allowed us to measure the tonsillar descent over time. After the first epidural blood patch, there was a clear radiological improvement. However, this response was not sustained because by 5 months, the patient's symptoms put us in a position where we had to repeat the epidural blood patch. This time, we did not do it in the sacral hiatus, rather in the classic lumbar epidural space. We also injected a much larger amount of blood and fibrin sealant. You can see a clear clinical and radiological response that lasted for the first two months. After the first two

months, symptoms did seem to worsen slightly again, but interestingly, there was still some persistent response to the procedures for the next few months.

Looking specifically at upright tolerance, however, there were lasting positive effects to the injection. Before the larger blood patch injection at 5 months, the patient could only stand for about 3 minutes before she would have to sit down. After the procedure, the patient reported that she could stand for 120 minutes. This result was concurrent with the improvement of tonsillar herniation on radiological image at 6 months in **Figure 4**.

An interesting point is that there may be some level of sustainability with repeated epidural blood or fibrin injections. We observed a persistence of moderate symptoms following the second blood patch; the symptoms did not become as severe as they had been at first. (**Figure 4**) We hypothesize that repeated injections may lead to fibrosis in the area, changing the compliance of the epidural space. Repeated injections, therefore, may lead to a greater amount of symptomatic relief for a longer period of time.

Advancement in Epidural Blood Patches

The classical approach to epidural injections is through the lumbar space but, increasingly, medical professionals are considering that perhaps the lumbar space is not the correct location for epidural injections.[15] If you look at patients in whom you can actually define a location of CSF leakage, you may notice that a lot of these patients do not have leakage in the lumbar space. Rather, they have leakage in the cervical and thoracic epidural spaces. The question becomes, if the epidural injection was done somewhere between the cervical and thoracic junction, would you have a better response to the intervention?

I am going to show a variety of cases in which we tried cervical epidural treatments. The cervical epidural blood patch is a procedure that we have recently adopted with greater frequency. The first case I will describe was a 57-year-old man, presenting with severe headaches thought to be consistent with intracranial hypotension. The patient had two lumbar epidural patches, with no clinical response. The decision was then made to try the cervical epidural patch to see if the patient had a better and, hopefully, more sustainable response.

The procedure is done while the patient is awake, and is performed under fluoroscopic guidance in the lower cervical space— the C5-6 interspace. Like any procedure, we begin with 10cc of 1% lidocaine injected for a local anesthetic effect. The goal is to enter into an interspace from the dorsal aspect, all the way into the epidural space. To make us feel more comfortable inserting anything into the cervical space, we purposefully use a smaller needle (20 gauge x 15cm) for the cervical epidural injections. The needle position is checked under fluoroscopy and then the needle is advanced just left of the C5-6 at midline into the lower cervical compartments, in small increments, up to the ligamentum flavum. We started doing this procedure in the lateral decubitus position because it was difficult to get the shoulders out of the way in the prone position in order to visualize the interspace, particularly in the lower cervical region. Then identifying the epidural space is similar to any epidural space identification, where a loss of resistance is considered a mark of entry into the epidural space. As with other procedures, small injections of air are used to check

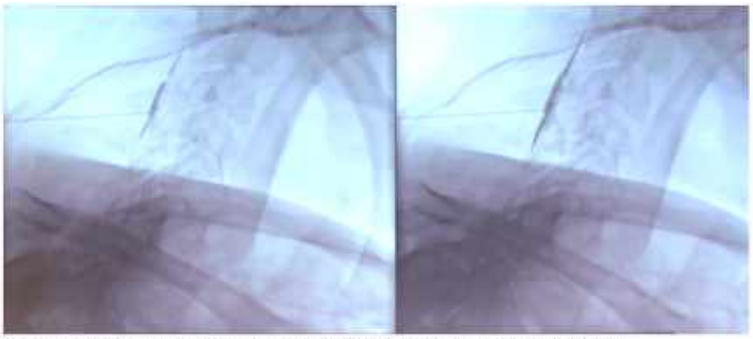

Figure 5. Contrast injection testing to ensure epidural space is reached.

if there is still resistance; and as soon as the epidural space is entered, there will be a marked loss of resistance. In **Figure 5**, you can see that the epidural space has been outlined with contrast. This allows us to confirm that we are in the epidural space.

Subsequently, blood is injected. When we started doing this procedure, we needed to determine how much blood to inject. In the lumbar space we are comfortable injection up to 30cc. However, the dilemma for the cervical epidural space is that we do not want to inject so much blood that we are mimicking an epidural hematoma, which could result in spinal cord compression. So far, we have only injected up to a maximum of 18cc and we have seen no neurological symptoms or evidence of spinal cord compression as a result. Dynamic CT imaging later showed contrast layer (blood) contained entirely within the epidural space, mainly in the posterior component of the epidural space.

Results of a Small Case Series: Cervical Epidural Blood Patches in Persistently Syndromic Patient

We have now done four of these procedures on patients who had a failed response to a previous epidural blood patch injection in the lumbar region. We monitored the results of the procedure carefully with an independent physician, who documented the responses. **Table 2** shows our results.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Age/Gender	57 M	35 F	35 F	37 F
Presenting symptoms	Occipital headaches, worse with prolonged standing	Bi-temporal continuous headaches with occipital radiation	Chronic severe headache radiating to mid-thoracic spine with vomiting	Right eye and facial pain with radiation to adjacent areas
Pain intensity	8/10	10/10	10/10	9/10
Insertion level	C5-C6	C5-C6	C4-C5	C5-C6
Post-procedural complications	Dull pain in posterior neck and anterior chest wall 20m post-procedure	None	Pain at cervical blood patch location with myoclonus	Intractable headache relieved with oxycodone
Clinical response	Full resolution: intensity 0/10	Full resolution: intensity 0/10	Partial resolution: decreased severity/frequency	Partial resolution: frequency (2/d vs. 5-10/d)
Duration of clinical response	1.5 weeks	3 days	1 week	3 weeks

Table 2. *Results.* Cervical epidural blood patch in patients with persistent symptoms following previous lumbar blood patch.

All four patients had some response to the cervical epidural injection. The individual responses, however, varied. Some patients reported complete resolution of symptoms, while others reported partial resolution. The duration of the clinical response also varied.

The most important result from this small sample, however, was in terms of the complications. The only complication that we observed was localized pain following the procedure. We did not observe any epidural compression or spinal cord compression, at least based on the amount of blood that we injected into the cervical epidural space.

Blood Substitutes

The last thing that I would like to quickly highlight is that we have always used this term "blood patch," but that is really a misnomer. Most of the time, these types of injections now use blood substitutes.[16] In fact, there is more data coming out indicating that, more often than not, it is *platelet rich plasma* being used to inject into the epidural space. Blood banks generally do not carry whole blood anymore. Instead, you can get a combination of plasma and platelets and mix them. To get 20cc of platelet rich plasma, you will combine 6cc of platelet concentrate, 12cc of thawed fresh frozen plasma and 2cc of Isovue 200 M contrast agent.

One reason that we use platelet rich plasma rather than autologous blood is that it is sterile. For instance, for patients with meningitis who then develop intracranial hypotension because of a lumbar puncture, it would be ill-advised to use autologous blood for the blood patch, given the risk of epidural abscess. Instead, the platelet rich plasma is used as a substitute. Additionally, platelet rich plasma also has growth factors. So, there may be some role in the actual healing of the epidural space over time.

Again, fibrin glue has been used for patients where a more sustained response is required. Unlike blood, fibrin will not be hemolyzed, so it remains for a long period of time. However, you have to be aware that it may cause epidural fibrosis which may be a concern in people who have repeated epidural injections since the epidural space becomes less and less available for further injections.

Conclusions

I am going to conclude with the following statements. The upright posture intolerance is an important component of intracranial hypotension and other diseases yet not as widely recognized and not quantified. Contribution of positional changes in cerebral venous drainage and variations between individuals in upright posture intolerance requires further study. Quantitative assessment of various components of upright posture intolerance is important. I believe we need long term studies to understand the therapeutic effects of epidural blood patches in patients with Chiari malformation and whether a relative period of stability can be achieved with repeated injections. Cervical epidural blood patches may be valuable in patients who have refractory symptoms, but I think that patient selection criteria still need to be defined.

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3.

Inheritance of Small Posterior Fossa in 2 Families Affected by Chiari I Malformation

JOHN D. HEISS, M.D.

Introduction

I am a neurosurgeon, not a geneticist, and part of the team who authored the article, "Inheritance of a Small Posterior Fossa in two Families Affected by Chiari 1 Malformation." This project was a collaboration with Dr. Enver Bogdanov and others, including Dr. Anthony Musolf, a very talented post-doctoral fellow and first author of this article.[1]

This project started when Dr. Bogdanov contacted us explaining that he had found a higher prevalence of Chiari I malformation in a village in the Tartar Republic, Russia. We also collaborated with Dr. Joan Bailey Wilson who is a statistical geneticist at the Human Genome Research Institute.

By means of quick overview, our method first involved phenotyping members of families with over two members affected with Chiari I malformation into groups: those affected with Chiari I malformation or a small posterior fossa, and those unaffected. Then we conducted whole genome sequencing on the same family members. After that, we performed a linkage analysis to determine which genetic markers were linked to the Chiari I malformation phenotype and which were linked to the small posterior fossa phenotype. We found linkage between the small posterior fossa phenotype and markers in a single chromosomal region in each of the two families. I will elaborate on these findings today.

Background

We planned our study after reviewing the work of Dr. Tom Milhorat and Dr. Marcy Speer reported in their 1999 paper on the inheritance of Chiari I malformation in some U.S. families.[2] Apart from a few families, the Chiari trait was only inherited to the next generation. In the U.S., generally the pedigrees are quite small. As you know, if a phenotype is

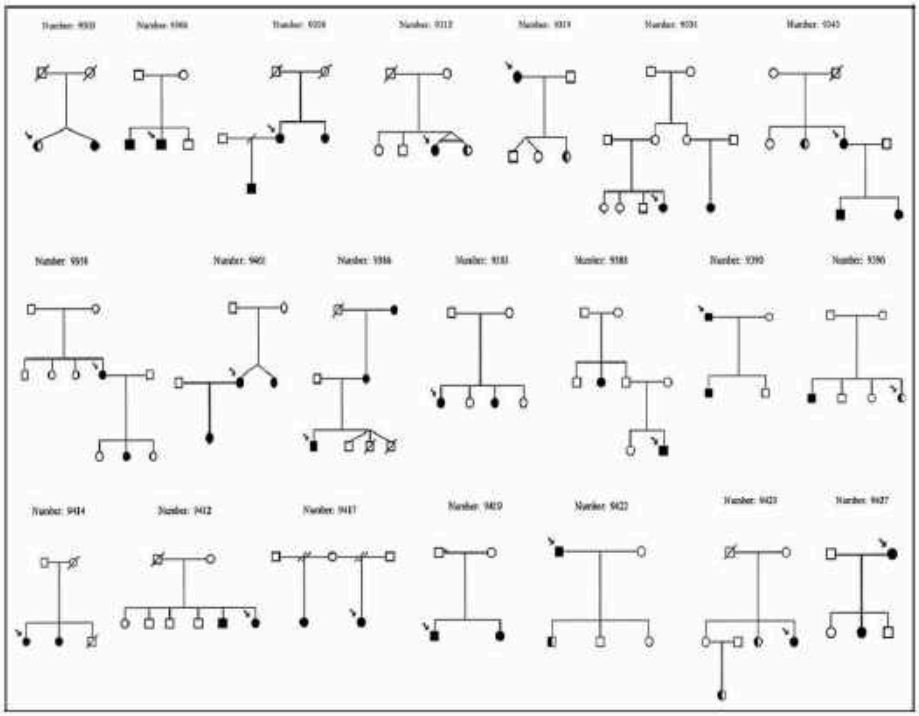

Figure 1. Pedigree from Milhorat et. al, 1999

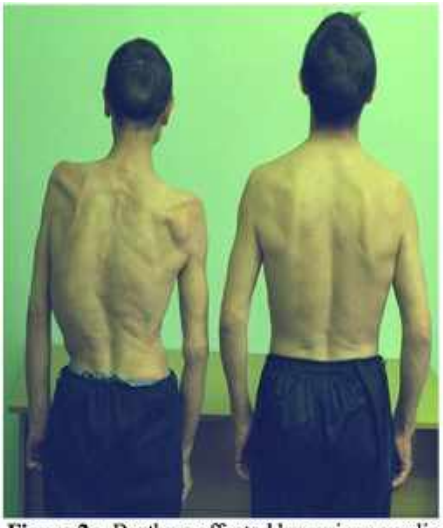

Figure 2a. Brothers affected by syringomyelia

not inherited from generation to generation, its origin could be environmental rather than genetic.

The first thing I asked when Dr. Bogdanov emailed us was, "where is Kazan?" Well, it is in Tartarstan, Russia. The Baltasy District was one small area in Tartarstan that had a high prevalence of patients with syringomyelia. In Kazan, neurological deficits are concerning, such as loss of pain and temperature sensation seen in syringomyelia. There is also great concern about Chiari and syringomyelia causing weakness in the hands because a lot of the people who live in that area are farmers. As symptoms worsen, they become less able to do their work. We also identified that Chiari I malformation occurred more frequently in the Tartars— an ethnic group within Tatarstan— than in the ethnic Russians.[3]

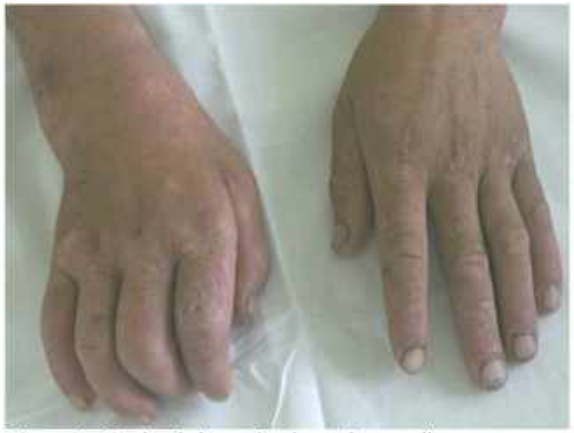

Figure 2b. Hand pathology related to syringomyelia

Our interest in this project continued to grow over time, resulting in 3 trips to Kazan and Tartarstan over many years. The publication was written after analysis of all the MRI and genomic data was complete.

On our first visit to Kazan, we saw things we don't really see in the U.S. much anymore. **Figure 2a** shows two brothers impacted by syringomyelia. The man on the left had syringomyelia for a little bit longer than his brother because of the scoliosis that you can see plainly in this image. **Figure 2b** is an example of a something sometimes referred to as "claw-hand" that results from syringomyelia damaging the cervical spinal cord. Painless burns were also common. The people of Tartarstan are, in general, stoic and resilient and many prefer not to undergo surgical treatment. They said, "Why should I have surgery? I can still work." A long period of natural progression is therefore seen in many of them, which is less often seen in the United States.

There were good reasons to do Chiari I genetics research in Russia. According to what Dr. Bogdanov told us and what we saw, the area of interest in this region of Russia was large; the regional prevalence of Chiari I malformation was about 100 times that of the United States. In this population, the Chiari malformation was mostly due to an under-development of the posterior fossa. Additionally, Chiari I malformation patients in villages were from geographically isolated populations. People rarely move out of the villages, so many of those in a village have a common ancestor. If this ancestor carried the Chiari I gene variant, it could be inherited and present at a much higher frequency than in other, less isolated populations. A higher frequency of a gene variant for Chiari I malformation in the population would make it more likely for Dr. Wilson to find this gene variant. And as I mentioned before, Chiari occurred in the Tartars and not the ethnic Russians even though they have similar environments, leading us to believe that Chiari I malformation was arising from an identifiable genetic, rather than an environmental effect.

Objective

Our study objective was to find a linkage between a genetic region and the small posterior fossa phenotype on a genetic map. It is believed that a small posterior fossa is one of the underlying structural deformations that contribute to Chiari malformation and that it is associated with shortening of various bones in the skull. Once we established phenotypes for family members, we would do whole exome sequencing. Chromosomal regions with genetic markers highly associated with the small posterior fossa phenotype were considered linked. We have not yet sequenced the area around the linkage to determine the involved gene.

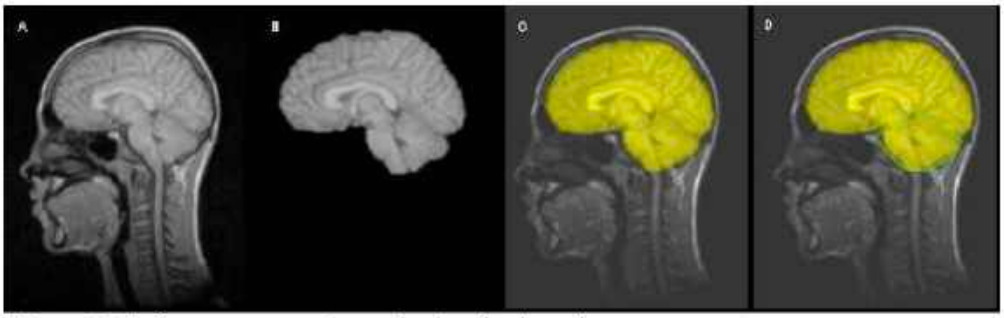

Figure 3. Software was used to calculate brain volume

Methods

We had 52 individuals from 7 families in our study, all from Russia. We enrolled some U.S. families in the study, but we did not find any linkage, so they were excluded.

On patients without a spoiled gradient recalled (SPGR) MRI scan, we measured the posterior fossa structures on T1-weighted MRI scans of the brain. For the Russian patients, we took the special measure of translating the protocol consent documents into Russian. Our criteria to establish a phenotype for small posterior fossa included: either a basi-occiput length <21 mm, or a clivus length <40 mm with a suboccipital bone length <38 mm.

For those who did have SPGR MRI scans, we defined a small posterior fossa as a posterior fossa volume of less than 15% of the intracranial volume. We used software to establish intracranial, posterior fossa, and brain volume as shown in **Figure 3**.

For the *whole exome sequencing* (WES), we collected 20 mL of venous blood for genomic DNA. About 500,000 genetic markers were used. The geneticist assured quality control.

After we had collected the posterior fossa measurements, we dichotomized them to phenotype subjects as either having a small posterior fossa, or a normal posterior fossa. We also dichotomized subjects into those who are affected or unaffected with Chiari I malformation. We performed the linkage analysis between the WES genotype data and the posterior fossa phenotype data. We measured the clivus, the basi-occiput, and the suboccipital bone. In some patients it was difficult to find the clivus synchondrosis to measure the length of the basi-occiput.

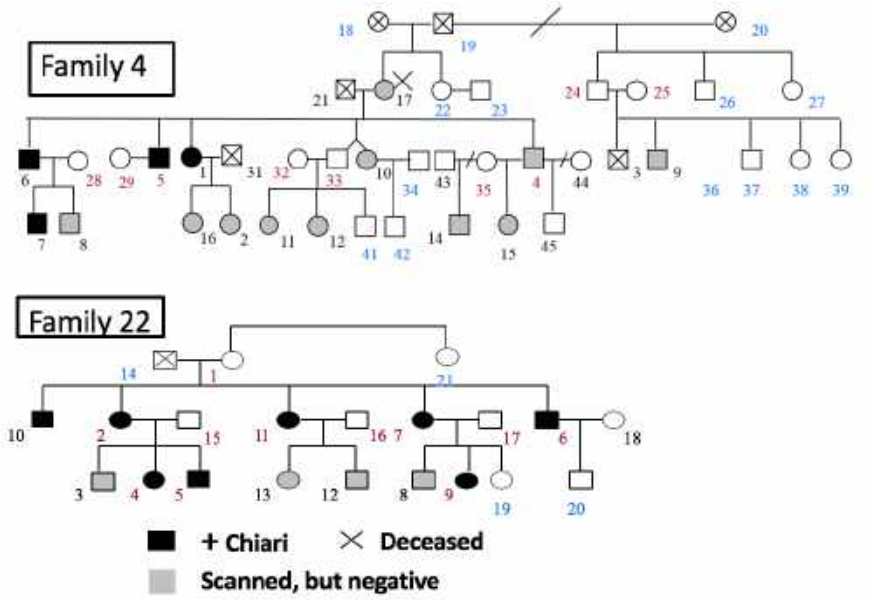

Figure 4. Chiari I family pedigrees

Figure 4 illustrates the family pedigrees for the two families with linkage. We found that the trait for small posterior fossa is inherited from one generation to another. In some cases, it appeared to act like a dominantly inherited trait.

Linkage Analysis

Adjacent alleles on the same chromosome tend to be inherited together. Understanding the crossover and recombination of maternal and paternal chromatids that occur during meiosis allows us to "map" genes using linkage analysis. This is a type of analysis wherein we can locate a gene by identifying which genetic marker segregates with the disease in families. It is measured in logarithm of odds (LOD) scores for each family.

It is harder to have crossover of two genes that are very close to one another on the same chromosome, in comparison to two genes that may be more distant on the same chromosome. The less frequently the gene recombines (crosses over to the other chromosome), the closer those genes and their markers are on the chromosome in question.

For example, in **Figure 5**, shaded circles and squares represent females and males, respectively, who are affected by the disease of interest, in this case, Chiari I malformation or small posterior fossa. Unshaded circles and squares are those females and males who are unaffected. In this example, we may notice a trend that those individuals affected by Chiari, or small posterior fossa on this pedigree (shaded) also tend to inherit the 'red' allele.

Given that we know that genes that are located nearby on the same chromosome tend to crossover together, this implies that the disease locus is likely close to the marker locus on the

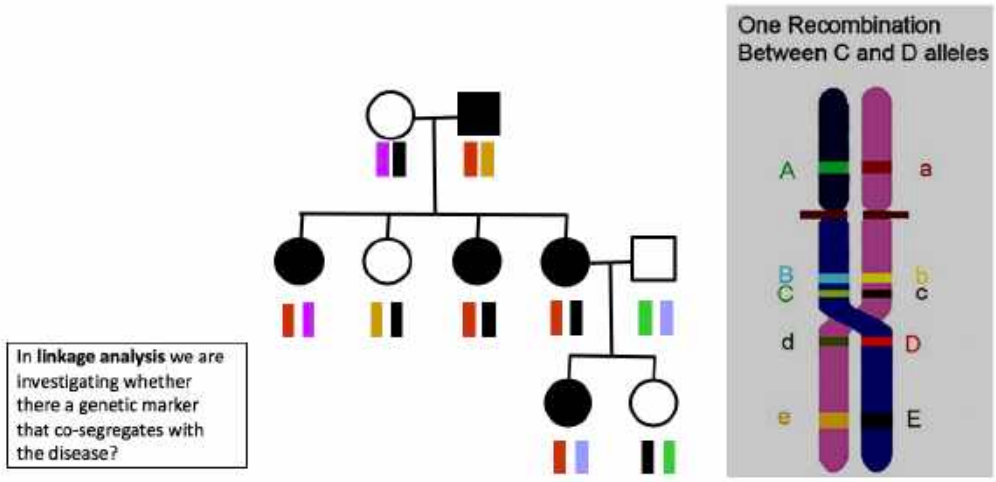

Figure 5. *Linkage co-segregation*. Shaded circles/squares indicate disease (small posterior fossa) and the bars below each represent two inherited alleles. In this example, we notice that disease seems to track with the inheriting of the 'red' allele, implying that the disease locus is found near the marker locus on the red allele.

same chromosome. This fictional gene on the 'red' allele, then, is more likely to be related— or "linked"— to the gene that causes small posterior fossa in this family.

I am going to show you the linkages that we found between some of the variants (SNVs). There was linkage between the small posterior fossa and the individual SNVs. The other was a linkage between a small posterior fossa and individual genes, the chromosomal loci. The model parameters that were assumed were as follows: autosomal dominant mode of inheritance, disease allele frequency of 1%, 80% penetrance for carriers, and no phenocopies.

Results

A LOD score of >3 generally indicates statistically significance. A log(3) is 1:1000, meaning the situation in question would occur randomly in less than 1000 cases.

First, we assessed the combined family LOD scores for linkage. **Figure 6** shows a "hit" on chromosome 1 in both the variant- and gene-based analysis. There is a strong variant based peak at 1q43 (HLOD = 3.5). For the gene-based signal, the LOD score is over 3 again at the same location (HLOD = 3.2). In the variant based LOD scores, we also saw a highly suggestive signal at 12q23 (HLOD = 3.25). For the gene based LOD scores, we also saw signals at 12q23 (HLOD = 4.4) and a new, strong signal at 1p32.2 (HLOD = 4.8). Overall, these results look very promising.

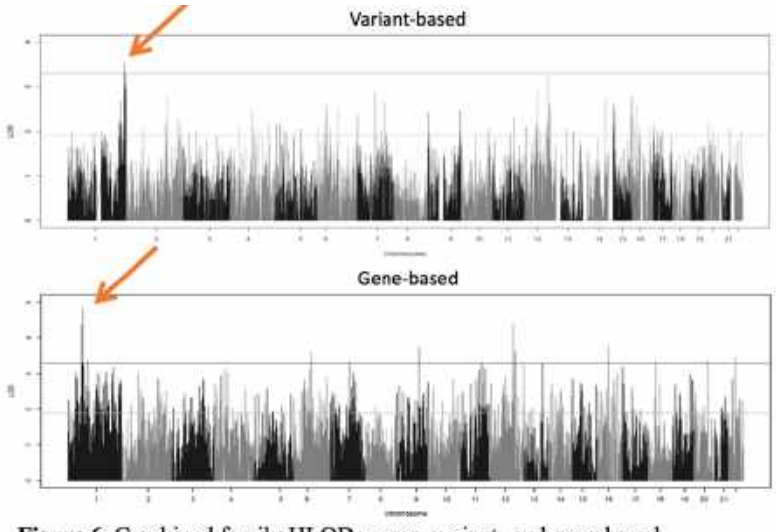

Figure 6. Combined family HLOD scores, variant- and gene-based.

When we looked at Family 4, specifically, there was

a peak and a LOD score above 3 on 1q43, again. For variant-based autosomes, there was a maximum LOD score of 2.9. In this region, eleven SNVs (exonic, intronic and UTR), and five single-nucleotide polymorphism (SNPs) had minor allele frequency (MAF) thresholds of about 0.01. For gene based, we saw a maximum LOD score of 2.9.

Figure 7 shows our chromosomal fine mapping. We use fine markers when there are large areas of interest for linkage. These areas included *SMYD3, AKT3, COX20, CEP170* as potential candidate genes. We cannot say these genes are directly involved. All these genes could be involved with bone metabolism. For example, *SMYD3* codes for histone methyltransferase accounting for DNA production and translation. Cell proliferation and differentiation, cytochrome c oxidase and centrosomal protein are encoded for by the genes *AKT3, COX20* and *CEP170*, respectively.

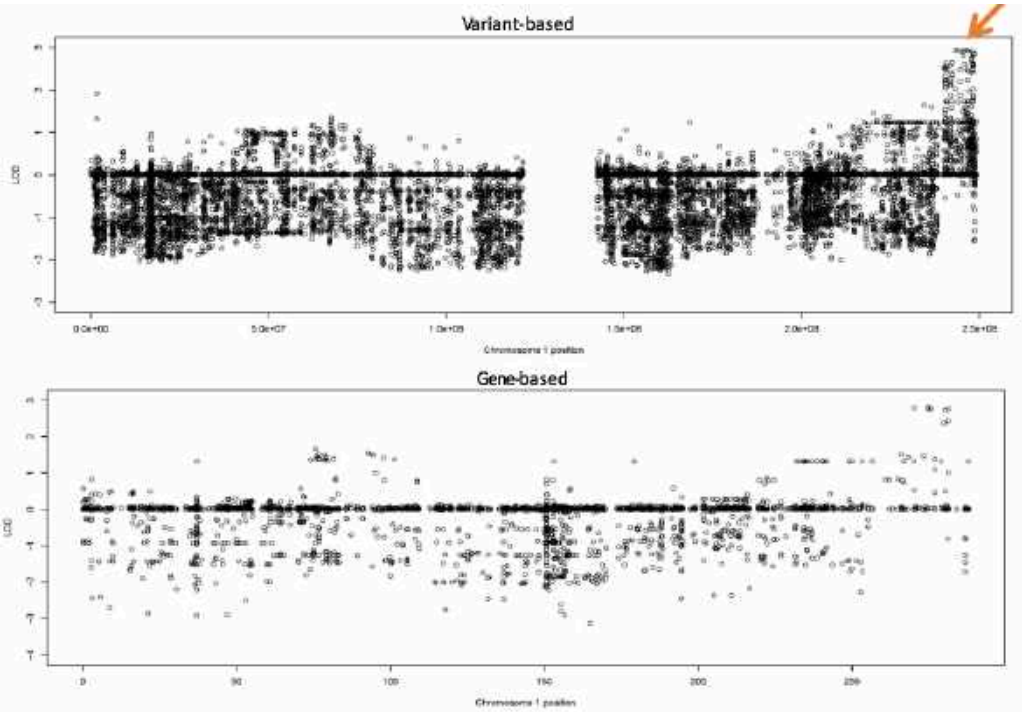

Figure 7. ***Chromosome fine mapping.*** Long-linked haplotypes; Genes of interest include: ***SMYD3*** (histone methyltransferase), ***AKT3*** (cell proliferation/differentiation), ***COX20*** (cytochrome c oxidase), ***CEP170*** (centrosomal protein)

Interestingly, we also found linkage in Family 22, but on a different chromosome; this linkage was identified at 12q23. The LOD score was 2.4, so not as high as the previous linkage, but still worthy of discussion. On the chromosomal linkage map for genes of interest, there were some particularly intriguing candidates. For instance, *TMEM119* is responsible for bone formation and mineralization, which are processes that if disrupted by a variant in a Chiari I malformation gene could result in development of a small posterior fossa. Other candidate genes included *DRAM1* encoding for DNA damage and repair and *SSH1*, which is an actin-binding gene that is implicated in connective tissue disorders.

In review, we analyzed seven extended families and found linkage in two. (**Figure 4**) Three to four successive generations of these families had Chiari I malformation or small posterior fossa upon our phenotyping. Upon performance of WES and parametric linkage analyses, we found a genome-wide significant signal in both linkage analyses to the small posterior fossa phenotype of chromosome 1q43-44 (HLOD = 3.5) and 12q23 (HLOD = 3.3). Each linkage peak we found was driven, almost exclusively, by one of two families (Family 4 or Family 22).

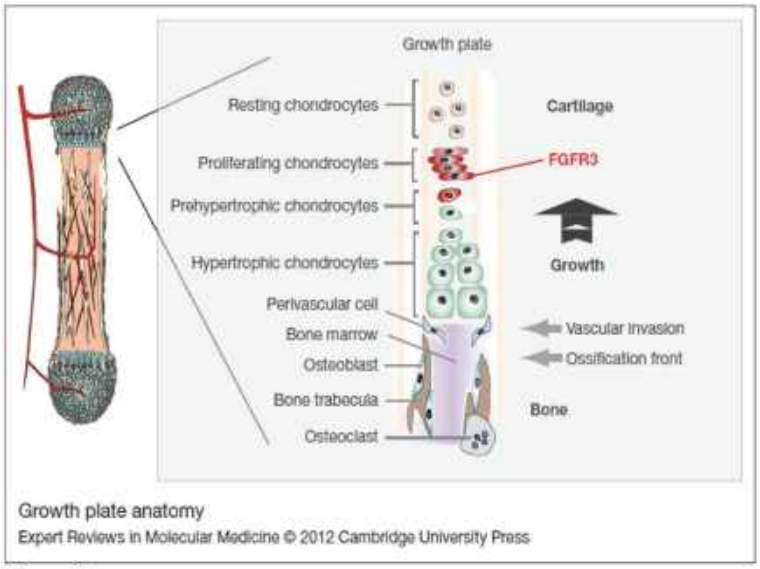

Figure 8.

Both regions identified in this work contain several linked exonic variants, including rare variants located in candidate genes that may impact posterior fossa development, and therefore, may be implicated in Chiari malformation. We also found that each family had a different chromosomal locus involved with Chiari, which was interesting.

Future Directions

An ongoing step is to complete even finer linkage analyses to find the specific genes affected in regions where we already found linkage to small posterior fossa in families with many members affected by Chiari I malformation. Of course, these families realize that Chiari I malformation runs in their families, and certainly, they would like to know why this is the case. So, to learn more, we are going to look more at candidate genes to better understand their involvement in the bone development process. Any genes implicated in **Figure 8** may potentially be involved and will need to be analyzed more closely. Indeed, *FGFR3* has been implicated in the development of achondroplasia. We hypothesize that Chiari I malformation in the two affected families results from loss of function of other bone development genes.

Conclusions

In conclusion, we found linkage signals in two families for small posterior fossa, a probable cause of Chiari malformation, at chromosomal loci 1q43-44 and 12q23. We have not identified the affected genes yet, but because these two regions have multiple candidate genes that could logically be implicated in the development of Chiari malformation. Linked haplotypes extend across broad chromosomal regions, making identification of causal genetic variants more difficult.

Next steps include functional analysis and animal models, looking at other phenotypes of Chiari malformation (e.g., reduced suboccipital bone length, reduced clivus length, or reduced cisterna magna AP width), and Copy Number Variant (CNV) analysis. Thank you very much.

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4.

Rare Functional Variants in Chiari Malformation Patients

ALLISON ASHLEY-KOCH, PH.D.

Introduction

I am a genetic epidemiologist who has been interested, probably for over a decade, trying to find genetic variants predisposing individuals to Chiari. Our group has published a couple of papers over the years. Primarily, most of what we have published up to this point has to do with some more broad regions across the genome that could contribute to risk through certain genetic variants. Those of you who are familiar with genetics will know that these are fairly common genetic variants that may or may not have a functional role. The genetic tools that we have are constantly improving and now we are starting to look more at rare genetic variants, particularly those that are functional.

Just in the interest of time, I will skip the background and definition of Chiari because I am pretty sure the individuals in this audience know what Chiari is. Why are we interested in studying Chiari? We certainly understand the mechanism of the disease very well, but from a genetics perspective, we cannot predict very well the genetic inheritance of Chiari. Of course, ultimately, it would be wonderful if, through a better understanding of these genetics, we could develop genetic tests for more accurate and earlier diagnosis or even help us develop new therapies and approaches to treatment.

Evidence of a Genetic Component

What do we know about genetics and Chiari? We know that there is some familial aggregation. There are anywhere from 10-20% of cases that report a relative or a family member who has a formal diagnosis or similar symptoms. Our group at Duke has collected data from over 200 families who have one or more relatives that also have Chiari. There have also been a number of twin and even triplet studies. There has been a high concordance among identical twins since they share 100% of the genetic material.

To move more into the discussion I will focus on today, there are a lot of reports of Chiari co-occurring genetic syndromes. Some of these syndromes are Ehlers-Danlos syndrome (EDS), Marfan syndrome, Klippel-Feil syndrome, growth hormone deficiency, craniosynostosis, and neurofibromatosis type I. Looking at previous Chiari malformation family studies, we also see evidence that there is linkage on chromosome 9 and 15 and that posterior fossa volume and basal angle are heritable traits. I will specifically point out the Boyles reports because that one was one of the first to look at common genetic variants.[1]

Mechanisms of Tonsillar Herniation

We know that there is no single mechanism for Chiari malformation. There is clinical heterogeneity within Chiari malformation which probably contributes to the genetic heterogeneity. So, there are a lot of patients who probably have a classic Chiari malformation where there is cranial constriction, resulting from a small posterior fossa possibly due to an underdeveloped

occipital bone. We also believe, however, that there are some patients who have Chiari malformation as the result of different mechanisms such as in cranial settling, wherein the occipital bone and posterior fossa volume are normal but there is cranio-cervical instability. Patients who have an etiology resulting from cranial settling are particularly likely to have co-morbid connective tissue disorders.[2] These connective tissue disorders including EDS, Marfan syndrome, et cetera are, in these cases, frequently co-morbid with Chiari. We have known this for a while. Even more recently, we are finding that these connective tissue disorder co-morbidities are also associated with differences in cranial morphology.[3] Our group previously showed that these co-morbidities are also related to Chiari I malformation.[4]

Sequencing

As I had mentioned in the beginning, previously we were looking at common genetic variations. Now, with the more current technologies that we have available, we are moving towards studying rare variations using *targeted next generation sequencing*. What we have done is focus on 21 genes that we prioritized from previous work and EDS. From these studies, we identified methods to target specific exon regions for each of those genes. We targeted the exons, rather than the introns because the exons were protein encoding for those particular genes. We wanted to identify rare genetic changes but also those that are potentially functional, meaning those genetic changes were likely to impact the protein that would possibly cause Chiari.

Our aims, therefore, for determining the relationship between genes were two-fold. Firstly, we wanted to see whether or not, in Chiari patients, there were more rare genetic variants for any specific genes. Secondly, we wanted to determine whether, within the Chiari patient groups, there were any genetic differences between those who did or did not have connective tissue disorder symptoms.

Dataset

Our data set was a little less than 200 patients (N=186). They were all female, non-Hispanic white and ranged in age from 18-years-old to 82-years-old. We defined their connective tissue disorder status using the Beighton score scale. Patients with ≥6 on this scale or those with connective tissue disorder-associated symptoms such as hypermobility, mitral valve prolapse, aneurysm and kyphosis were considered to be affected.

The data set was really composed from two different sources. One was the Chiari 1000 cohort collected at University of Akron and sponsored by Conquer Chiari and the other was a subset of the Duke cohort. The Duke data subset was selected to match the patients that were in the Chiari 1000 dataset. The Chiari 1000 dataset was almost exclusively white non-Hispanic women. This is what drove the selection of patients for the Duke dataset match. You will see that the Duke dataset has a higher percentage of patients with connective tissue disorders. The two data sets were pretty similar in the percentage of patients with a formal diagnosis of EDS. The Duke dataset also had a slightly higher percentage of patients with syringomyelia. We tried to match the Chiari 1000 dataset as best we could.

Results

At the end of the day, when we looked at the 21 genes, we picked up 1,345 total variants in those datasets. A subset of those were exonic (777) and, of those, 489 were predicted to be functional. Most of these variants were common and already identified in public databases and were unlikely to be associated with Chiari malformation.

Figure 1 shows the number of variants that were identified per gene: the bars on the left represent all the variants identified and the bars on the right represent the variants that were predicted to be functional.

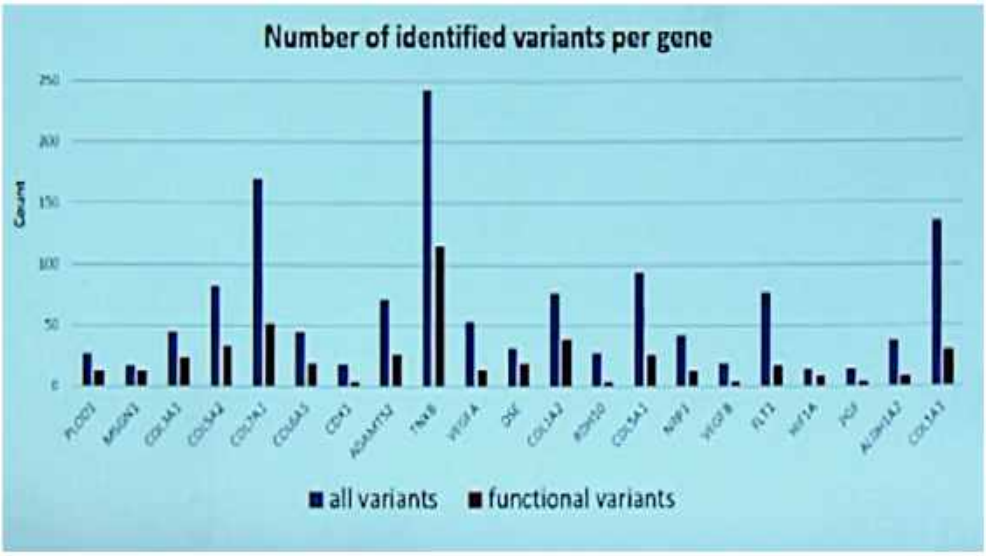

Figure 1. Number of identified variants per gene

Our major first question was, is there an excess burden of rare, functional variants in Chiari malformation patients compared to controls? We did not really sequence any controls, so we had to rely on public data for our controls. This came from gnomAD— a Finnish European database.

We found that there were several genes with an increase in rare functional variants in Chiari patients compared to controls. **(Table 1)** It was interesting that a lot of those variants fell into the collagen genes. This was really exciting for us and we will talk a little more about that. Interestingly, a quarter of the patients with Chiari have a rare coding variant in the gene *COL6A5*, which was our strongest signal. Nearly 50% of Chiari patients had a rare coding variant in one of these collagen genes: *COL5A2*, *COL7A1*, *COL6A5*, and *COL1A2*. We then wanted to see if there is a variant in one of these genes. The odds of having Chiari malformation, given a genetic variant were reported as odds ratios. Given a particular gene, the individual would be anywhere from around 2 to 8 times as

Gene	N SNPs	P-value	Odds Ratio
COL5A2	12	0.0001	1.814
COL7A1	14	0.0006	2.424
COL6A5	23	<0.0001	1.99
COL1A2	3	0.0095	8.273
VEGFB	3	0.0036	7.436
FLT1	8	0.001	3.354

Table 1. Gene burden in CMI vs. controls

likely to have Chiari malformation. Some of these variants have strong effects.

Our second major question assessed any excess burden of these functional variants in Chiari patients with connective tissue disorder symptoms, compared to those without. We did pick up two genes where we saw something that was interesting. Again, the variants appeared to be restricted to the collagen genes. For *COL3A1*, we saw patients who had an increase in connective tissue disorder symptoms, had a lower percentage of variants in that particular gene. On the other hand, those who had connective tissue disorder symptoms had a higher likelihood to have a rare functional variant in the *COL7A1* gene.

Discussion

What do these genes have to do with Chiari? We were really excited about the collagen genes because they are expressed in the brain, spinal cord, skin and bone. These genes are expressed in a lot of tissues that are relevant to Chiari malformation. They help to make up the extracellular matrix, so they are widely expressed throughout the body. They have been known to be associated with a number of connective tissue disorders such as EDS (*COL1A2, COL5A2*), osteogenesis imperfecta (*COL1A2*), osteoperosis (*COL1A2, COL7A1*), infantile cortical hyperostosis (*COL1A2*), Ullrich and Bethlem myopathies (*COL6A5*) and epidermolysis bullosa (*COL7A1*). These conditions are sometimes found to be co-morbid with Chiari malformation.

The other pathway that we picked up was the *VEGF* pathway (*VEGFA, VEGFB, FLT1*). This is a growth signaling pathways, important for placental development in pregnancy and vascular development in general. This pathway cross-talks with the extracellular matrix genes and EDS genes; *VEGF* signaling may also contribute to the development of hydrocephalus.

Future Directions

The analysis done thus far was really based on functional predictions. There were a lot of software programs and models used in order to estimate the likelihood of particular of genetic variants being functional. To prove all of this, we will need to do some much more detailed molecular work. I also introduced the fact that there were associations with cranio-morphometric traits that seem to be different in Chiari patients with and without connective tissue disorders. The next step that we want to do is to look at these genes with respect to morphometric traits. Additionally, of course, would also like to expand our patient population in future publications. And lastly, we would like to look at more of the genome with this particular approach, since this study was performed preliminarily on just the 21 genes.

Conclusions

In large part, what we are starting to see is that there are a lot of other genes that are involved with Chiari malformation in a lot of different pathways. Additionally, we have found that Chiari malformation patients with connective tissue disorder symptoms may have very distinct biological mechanisms, as compared to patients who do not exhibit these symptoms. Finally, based on this work, the genes encoding collagen proteins and in the *VEGF* pathway are potentially strong candidates to predict risk of Chiari malformation. I am going to stop there and just acknowledge

my collaborators at Duke Molecular Physiology Institute, the folks that are part of the Conquer Chiari team at the University of Akron, and then, of course, Conquer Chiari who helped support this particular study.

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5.

Cases of Altered CSF Dynamics in Chiari Malformation

ERIC JACKSON, M.D.

Introduction

When Kaitlyn first approached me about giving a presentation at this meeting, it struck me that this is probably the right group where we could talk about our progress in neurosurgery up to this point and pose real questions about how we are doing insofar as the treatment and management of these types of disorders. In that vein, today I am going to discuss a specific group of patients in the hopes that we can have a dialogue about how we can improve our approaches in neurosurgery. I don't really have any disclosures, except that I did get a few slides from Dr. Luciano who gave a long talk about hypotension a couple years ago at a previous Bobby Jones CSF conference in New Orleans.

Hydrocephalus Following Chiari Decompression

The first case I'll present today I had encountered my first year at Hopkins. A teenager presented with classic syrinx symptoms. The symptoms included left-sided numbness; when she put her arm in the shower, she could not feel the temperature. She had normal ventricles on imaging at the time. We did, for me at the time, a standard Chiari decompression for a patient with a large syrinx. We explored the obex just to make sure there wasn't a web. We did not do anything to the tonsils other than spread them to make sure that there was a good outflow.

She did well initially. Her mother said she had stopped taking pain meds within a week of the surgery. However, she presented to an outside hospital two weeks after surgery with headache, malaise, nausea, and vomiting. She got a CT scan **(Figure 1)** which showed some fluid on top of the cerebellum and bigger ventricles. She was transferred to our hospital and we got an MRI. The posterior fossa looked pretty tight with a pseudomeningocele. We can also see, especially when comparing MRIs, that her ventricles had really come up. It seemed like she had developed subdural hygromas and what looks like hydrocephalus related to the Chiari decompression.

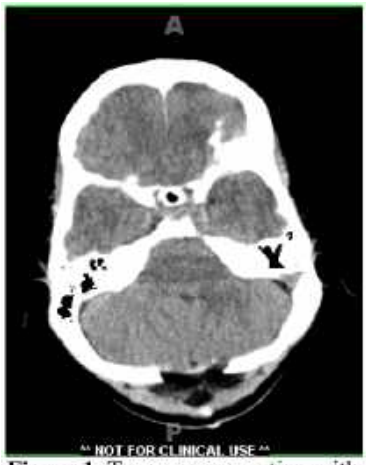

Figure 1. Teenager presenting with classic symptoms of syrinx

We asked ourselves, "Well, what do we do now?" I combed through the literature and a majority of them reported that the treatment involved drainage of the subdural spaces by putting in an EVD, or shunt placement.[1] The other papers I found spoke more theoretically about the problem: why do these subdurals happen? Theories for etiology of this phenomenon included the possibility that a small one-way valve in the arachnoid was responsible as a result of not opening it widely enough. Some people, therefore, advocate going back and doing a wide arachnoid opening. However, we did a wide opening the first time, so I didn't really think that was going to work in the case of our patient. Moreover, I think that a lot of us in pediatrics don't really like shunting for the sake of shunting, so I wanted to try something different, if possible.

Interestingly, however, when I went back and looked at the patient in question, the syrinx looked as if it were smaller after the surgical intervention, even though the radiologist didn't comment on it. What that suggested to me, was that there were probably some transient changes going on in this patient. I surmised, if we were able to get her through some of these new and particularly difficult symptoms, then they may eventually work themselves out without the need for additional surgery.

We chose to observe her in the hospital on a regimen of Decadron and Diamox. A week later, the tightness we had seen post-operatively at the foramen magnum had resolved and although her ventricles were not back to normal, they had started to come down a bit. I let her go home at that point and **Figure 2** shows her five-month follow-up scans. The syrinx is pretty much gone and the ventricles are back to normal. This is one of those situations where I really do not understand what was happening. At the same time, I think it is a good example where resisting the urge to overreact with surgical intervention likely yielded the best possible outcome for the patient.

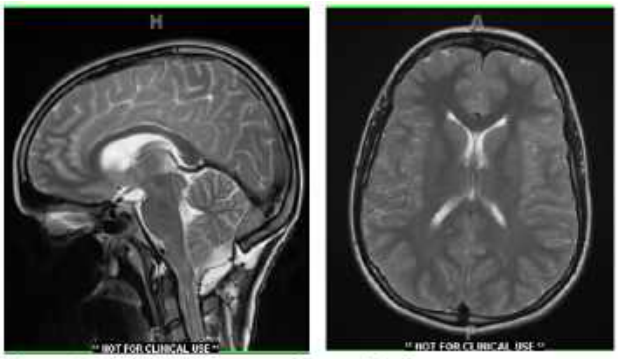

Figure 2. Follow-up scans after medical management.

My partner at the time, Dr. George Jallo, has since moved to Florida. Since his move, he has seen a number of patients that have experienced a similar situation. To ensure this got into the literature, we wrote a case series together. We described five different patients who had similar situations where they underwent Chiari decompression and later developed hydrocephalus or hygroma but were successfully treated for these issues via medical supervision rather than further surgery.[2] This is in contrast to previous literature which, as I have pointed out, are suggestive of shunting or draining.

Since then, I had a patient with similar finding although not as significant. A young girl presented with fairly classic imaging and Chiari symptoms including tussive headaches. We performed a Chiari decompression and cauterized the tonsils. In my practice, I feel that the patients with tonsillar reduction have the highest likelihood of developing chemical meningitis, so I tend to put them on a short course of steroids. As her steroids tapered off, she presented to the ED with a worsening headache. There was a small pseudomeningocele and her ventricles were a little bit bigger. Again, I didn't really understand why. Since the imaging findings weren't as significant as the other patient, we just prolonged the steroid taper and put her on a short course of Diamox. The symptoms improved and her ventricles returned to baseline on imaging.

I think this is just one of those things we talk about in Chiari— there have to be alterations in CSF flow, probably both as an antecedent to disease and subsequent to surgery. It is still a little unclear to me what the exact physiology may be, but it likely has something to do with the fact that we are opening something to the outside world that is usually a closed system. Amongst neurosurgeons, there is such a huge variety in what people do surgically ranging from bone-only decompressions to duraplasty with tonsillar reduction. There are even differences in how the dura

is closed; some surgeons leave the dura open without any patch. With so many variables left unstudied, we do not understand the etiology of these changes. I think the important thing in looking at a lot of these patients is that these changes can be transient. Allowing the body to have the opportunity to fix things itself with close monitoring can be beneficial. Attempting conservative therapy first may allow us to avoid further surgical intervention down-the-line.

Hypotension and Chiari Malformation

Still related to CSF dynamics, I want to shift a little to talk about CSF hypotension. A 21-year-old patient came to the hospital for a Chiari evaluation. He had two different types of headache. One headache was a classic Chiari headache: occipital headache, with straining. I follow Dr. Oakes' philosophy of trying to induce a headache in the clinic with Valsalva and in this patient's cases, it did provoke symptoms. He also had a right frontal headache, however. He reported that he doesn't really have this headache in the morning, but it gradually gets worse as the day goes on. Interestingly, I learned something new. This particular patient worked as a flight instructor and apparently the Federal Aviation Administration states that if you have any type of Chiari malformation you are not allowed to fly unless it has been treated. So, he came in pretty anxious to receive some kind of treatment from us because he really wanted to get back to work. The only finding on his MRI was the Chiari malformation. **(Figure 3)** He did not really have any of the other issues. There was no enhancement. The only finding consistent with CSF hypotension was the Chiari malformation itself.

So, the question for the neurosurgeon becomes: do you treat someone based solely on symptoms of low pressure with no radiological evidence other than Chiari malformation, particularly if classic Chiari symptoms exist? Chiari decompression, empiric blood patch, myelogram, and measuring of intracranial pressure (ICP) via lumbar puncture or monitoring are all methods that have been discussed in the literature in this type of case. Historically, a lot of these patients have had Chiari decompressions. Obviously, I think there are a lot of patients who have had Chiari decompressions who likely had a secondary Chiari, thus, probably did not have significant improvements in symptoms.

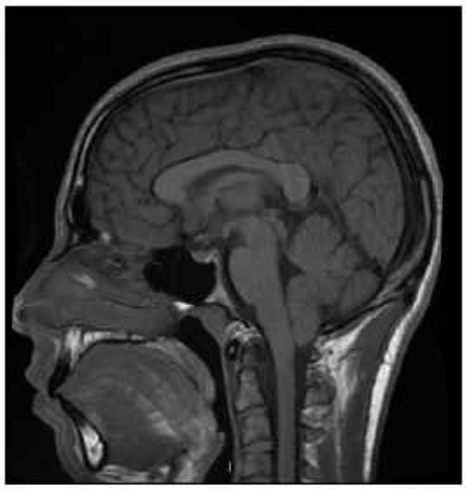

Figure 3. 21-year-old male with two distinct headache types.

This patient ended up getting a second opinion. He went to a well-known center with a national and international referral base. There they recommended an empiric blood patch followed by a myelogram pending the symptomatic results of the blood patch. Our interventional radiology group likes to do the myelogram upfront prior to blood patching with directed blood patches based on where they think they see a leak. We will also sometimes do blood patches with ICP monitors in place to look for improvements.

For anyone who is not aware, I want to briefly review the clinical and anatomical signs of CSF leak. A major clinical symptom is positional headache. Anatomical signs, largely based off

of the work done at Cedars Sinai, include **"SEEPS"** that can be seen on imaging. These include **S**ubdurals, dural **E**nhancement, **E**ngorgement of veins, **P**ituitary hyperemia and **S**agging of the brain. Obviously, Chiari tends to be part of the brain sagging, but there are other changes related to the optic discs, chiasm, or the brainstem as well. The sign that I often look for is the mamillopontine distance, I think that's an easy sign to find. Other signs of a sagging brain can include a flattened pons and smaller basal cisterns.

A paper from the Mayo Clinic in the late 90s described patients presenting with both Chiari and CSF leak.[3] Interestingly, all patients had the enhancement which makes the diagnosis easier. I think it is much harder to correctly identify and treat these patients when they don't have all of these "SEEPS" signs because it makes determining a treatment plan much more difficult to do.

When we look at statistics and numbers in the general population, I think the important thing is that the papers only include patients with a known diagnosis. If the diagnosis is often missed, then the numbers will be falsely low.[4] I will present a couple of cases that have all happened in the past couple of years. I think CSF hypotension is probably much more common than we know likely due to under-recognition. Symptoms of a CSF leak include headache, which is usually orthostatic, exertional, "end of the day", and it can often be exacerbated by sneezing, coughing and head movements. That is the hard part for me because it is similar to Chiari. Furthermore, it is often hard to make a distinction about whether the exacerbation causes the headache or makes the headache worse. There are other symptoms that do not include a headache like dizziness. Interestingly, there are a couple of papers that will talk about the lumbar puncture opening pressure often being normal and that was I asked in the previous presentation where the measurements are being taken. There is a paper out of the Duke talking about lumbar pressures.[5] Again, with this group they were doing something particular. They were doing a spinal tap before every patient. They recorded what they were doing and measured the pressure using an opening pressure of less than 6 centimeters of water as a diagnostic criterion.

Now, I think interpretation of these data is clouded by recent data on opening pressures in patients with a question of pseudotumor. I have seen a couple presentations recently, on this topic, for patients who have an LP for opening pressure and an ICP monitor. The data in these studies suggests the pressure on the ICP monitor is much lower than what it is measured via LP. They suggest for pseudotumor we can't trust the LP because it is giving too high of a pressure. Is it the same thing for hypotension? If your pressure is 10 on an LP, is some of that elevated based on the situation? Is it not really reflective of a normal pressure? If the opening pressure is not really reflective of intracranial pressure, it is useful diagnostic information?

This was the first patient that I saw in my practice that I made this diagnosis. Honestly the patients I see are primarily patients who come for a diagnosis of Chiari and, ultimately, I'm the one who's making the diagnosis of hypotension. The patient in **Figure 4a** came to me with classic symptoms of Chiari malformation. During the visit, she refused to Valsalva because

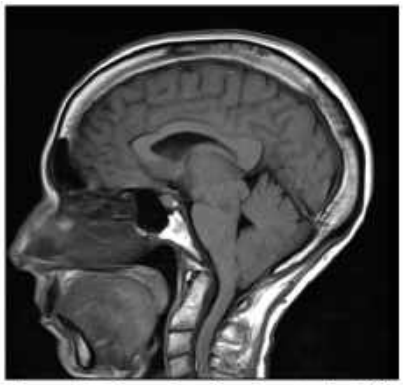

Figure 4a. Presenting imaging at the clinic.

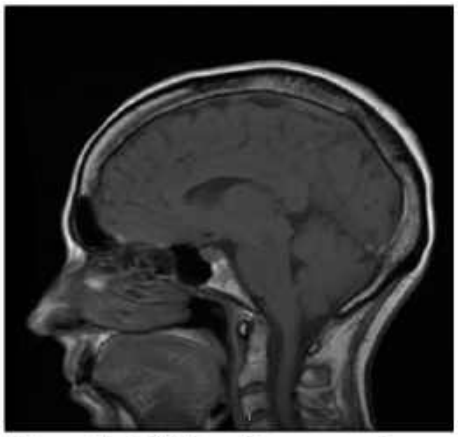

Figure 4b. MRI from four years prior.

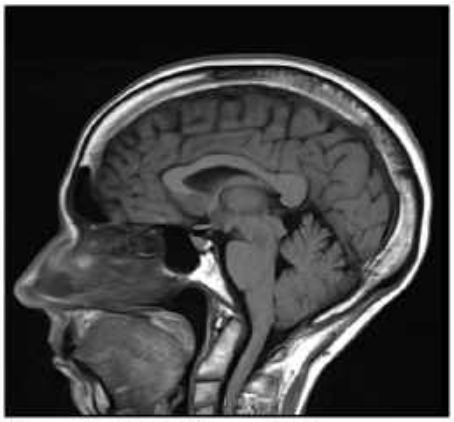

Figure 4c. MRI after medical management for hypotension

she said that it was going to give her significant symptoms. The thing that I initially noted on the imaging was the mamillopontine distance. The good news for us, was that she had an MRI done four years prior. We had her get that MRI and she did not have a Chiari malformation in that image. **(Fig. 4b)** At that moment, I knew I was not doing a decompression. We sent her to our IR group after obtaining an MRI that showed a diffuse leptomeningeal enhancement. As it turns out, she is a classic case of hypotension-induced Chiari malformation. She has had two directed blood patches. After the first one, she got better for about a month. She had another blood patch and then was better for longer. In the new MRI **(Fig. 4c)**, you can see the cerebellar tonsils had ascended and the enhancement had improved as well. Both her symptoms and her imaging improved.

Another patient had MS, and had been getting yearly MRIs. In between her MRIs, she developed headaches with straining and when bending over. On the more recent MRI, her cerebellar tonsils had descended further. Again, based on the imaging, from the moment we met, I knew that I was going to be referring her to interventional Radiology rather than doing a Chiari decompression. A separate patient came to the clinic recently in a similar scenario. She had a scan from 11 years ago which was normal and in the new scan she has a significant Chiari malformation with a decreased mamillopontine distance and leptomeningeal enhancement.

Now, those are all cases where it is relatively easy to make a diagnosis. On the other hand, you can see a patient like this who comes in with occipital headaches, dizziness, and questions whether she has POTS or other disorders as well as other symptoms. **(Figure 5)** She had seen another physician closer to home who said that there was no leptomeningeal enhancement and thus could not have low pressure. Patients like this one are the most difficult to diagnose and treat appropriately. On imaging, the Chiari malformation is not that significant, but there are symptoms with straining and also with positioning. Patients with this type of presentation are the ones in which we have started doing ICP monitors to avoid the question of where you zero the monitor in order to follow the pressure over time in all positions. Interestingly with this patient, when she laid down she had normal pressure but when she sat up her pressure went to -11. Based on data from the shunt patients that we treat, we know that negative numbers can be normal but our CSF disorders group feels that while -5 is within normal limits, -10 starts to be too low and there is likely a problem. Based on her readings, we ended up sending her for blood patching. Time will tell whether that is the appropriate treatment.

These patients are often the most complicated because they also often have features of dysautonomia. Then the question is, is it a cardiac issue? Fortunately, we have a neurologist who is interested in testing these patients, so she will do positional testing with these patients and

orthostatic vitals including: heart rate and blood pressure, as well as looking at the ICP. In the last patient, for instance, she thought it was probably a combination of POTS and dysautonomia with CSF leak indicating that the symptoms are likely multifactorial.

With multifactorial symptoms, the question then becomes, what is the best way to treat these patients? I think it is very easy with patients where the MRI imaging is clearly sufficient but is much more difficult for others who just have a Chiari on imaging but have some of these positional symptoms as well. I was discussing these patients with Dr. Luciano at some point, and I said, "When can I just do a Chiari decompression without other workup?". Again, I think there are probably patients out there who had a poor result from a decompression because they had a secondary Chiari and the source was not recognized. On the other hand, we cannot do myelograms and ICP monitors on every patient as that would be subjecting a majority of the patients to invasive procedures that are not necessary. I think we do not know the right answers now and I think that was one of my other reasons for wanting to talk about it and bring it up to a group like this. I think what we are doing with it now is really a combination of history and imaging. So, the patients who just have Chiari on their imaging but sound like they may have more hypotension than Chiari symptoms -- those are the ones to consider further work-up, including adding contrast to the MRI if it was not done. I think it is also important to discuss this dilemma with the patients so they understand and can be involved in the decision-making.

Conclusion

So, I will return to the 21-year-old that I introduced previously to make some final points. He had a second opinion recommendation for a blood patch followed by myelogram pending the results. Our interventional radiologist recommended upfront myelogram. Based on my discussion with my neurosurgical and neurology colleagues, I recommended ICP monitoring. This case highlights that our current knowledge is limited. Ultimately, I told the patient that we do not know the right answer and that I think any of these answers are potentially reasonable. I explained our logic and why we are making our recommendation, but based on current knowledge in the field, we cannot tell him that one recommendation is better than another. I am hopeful that as this disease process is recognized more, we will collect better data and be able to make more informed decisions. In this light, I thought I would present these cases because they are challenging, and I am open to the people's suggestions of how we could do better.

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6.

Measuring Outcome in Patients Undergoing Chiari Surgery

JOHN J. ORÓ, M.D.

Introduction

Thank you to Dorothy Poppe and the Bobby Jones CSF organization. This is a wonderful organization that, as you can see from the presentations today, is pioneering the next steps in patient care. Today, I am going to share our journey with outcomes in this area. I know this organization is very interested in progressing in that field. Of course, a lot of this work I have to credit today to Diane Mueller, ND, RN, FNP-BC for taking the lead in our efforts.

I think we all know the dilemma in treatment. There is little agreement on the best surgical treatment for patients suffering from the Chiari I malformation. Treatment outcomes vary widely and there is significant treatment failure.

Quality-of-Life Scales In Chiari Malformation, A Review

Early in the 21st century, we wanted to study our own surgical outcomes and we decided to focus on the quality-of-life before and after surgery. Does that answer everything? No, it doesn't but that's what we decided to pursue.

We searched for a quality-of-life questionnaire that would work well in the setting of Chiari malformation. We chose the *sickness impact profile (SIP)* since it was one of the most widely used scales in the literature.[1] It is a 136-item self- or interviewer-administered health status questionnaire. It identifies self-reported symptoms and functional status in three domains: physical, psychosocial and independent function. A number of domains is helpful in making sure that these scales are reliable because you want to look at a variety of different components. The twelve categories in the SIP are: Sleep and rest, emotional behavior, body care and movement, home management, social interaction, ambulation, alertness behavior, communication, work, recreation and pastimes, eating, and mobility.

We published the results of this study in 2005 for 112 of our patients. The SIP was administered both before surgery and post-operatively at one year.[2] We found improvement in 84% of our patients in self-reported quality-of-life ($p < 0.0001$) . Patient age, amount of tonsillar herniation, and the presence of syringomyelia did not correlate with the outcome. In other words, some patients could get better, could get worse or have either way.

After we got the results, I asked Dr. Mueller to call some of our patients who were not doing well (N = 16). Anecdotally, we wanted to see if there were any other factors that could be impacting their quality-of-life. At least four of those patients reported extraneous factors affecting their outcomes. One had a general health status change; another was an unrelated injury. One patient had an extensive thoracolumbar fusion for scoliosis that she was not doing well from. Lastly, one of the patients had lost her spouse and that greatly impacted her life. So, this taught us something important, and it is something that should be kept in mind as any proposed scales from Bobby Jones CSF are created. If we measure quality-of-life a year or two post-treatment, we do

Chicago Chiari Outcome Scale				
Pain	Non-pain	Functionality	Complications	Total Score
1 - Worse	1 - Worse	1 - Unable to attend	1 - Persistent complication, poorly controlled	4 - Incapacitated outcome
2 - Unchanged and refractory to medication	2 - Unchanged or improved but impaired	2 - Moderate impairment (<50% attendance)	2 - Persistent complication, well controlled	8 - Impaired outcome
3 - Improved or controlled with medication	3 - Improved and unimpaired	3 - Mild impairment (>50% attendance)	3 - Transient complication	12 - Functional outcome
4 - Resolved	4 - Resolved	4 - Fully functional	4 - Uncomplicated course	16 - Excellent outcome

Figure 1. *The Chicago Chiari Outcome Scale.* Aliaga et al., 2012.

want to have a questionnaire that at least helps us understand if there are other factors that could be contributing to that to change in quality-of-life.

Then there was a conference in 2008. I was there and so was Dr. David Frim. My presentation, interestingly, was centered around arriving at a consensus for surgery for the Chiari I malformation. Somebody had made a comment and I sort of just automatically blurted it out, "The problem is, we do not have a specific Chiari outcome scale." From that moment on, both our group in Colorado and Dr. Frim's group got to work pursuing this. Since then, we essentially have 3 Chiari-specific outcome scales that have been developed. I will touch on each of these scales right now.

Chicago Chiari Outcome Scale (CCOS)

Dr. Frim's group was the first to publish in 2012. That scale would become known as the Chicago Chiari Outcome Scale (CCOS).[3]

It is a fairly straightforward scale. **(Fig. 1)** There are 4-points in each category indicating the patient is worse, unchanged, improved, or resolved. The higher the point score on the scale, the better the patient is doing. The scale's categories include: pain, non-pain, functionality, complications and then the total score. The range for the total score is between 4-16. The higher the total score, the greater the improvement in those four domains. There has been some critique of this scale. Dr. Limbrick and his team at Washington University worked on that. We will touch on this later.

Chiari Symptom Profile (CSP)

When we were ready to develop our own disease-specific quality-of-life outcome score, we looked at the literature and found a number of other disease-specific scales. For example—and, again, this is instructive and important to consider in the creation of future scales— the *Impairment Scale* was initially developed in 1969, but then the American Spinal Injury Association (ASIA) group reformed and adapted it in 1982 to become the *American Spinal Injury Association (ASIA) Impairment Scale*. So, this is an excellent lesson: you can take an existing scale and adapt it to become a newer, expanded scale. Although I have not discussed this with Dr. Mueller yet, it is possible, for instance, rather than to develop an entirely new outcomes score, to instead adapt a

component of the Chiari Symptom Profile (CSP)[4], which I will talk about more in a moment. Nevertheless, there are a number of other scales that are disease-specific in other areas of neurological disease.

Before I discuss our development of the CSP, I want to clarify why we choose to focus on quality-of-life in assessing outcomes. Why quality-of-life? The answer is simple: quality-of-life is our moral imperative. The reason that we are here today and the reason we treat our patients is to improve the patient's perception of their daily life. The wording that we used in our article was as follows:

> The moral implication of medical intervention has led clinicians to examine quality of life as a significant outcome measure. The individual's self-perceived quality of life must imbue the opinions, experience, and expectations of the patient as the care recipient.

I think any outcome scale needs to consider the self-reported quality-of-life. There are a lot of people that contributed to this Chiari Symptom Profile (CSP). Kimberly Sexton, RN who assisted in data collection and Mary Siegrist our statistician, without whom we could not have done and completed this work. There was also a small grant from Conquer Chiari to support our statistical analysis. The CSP uses a Likert scale, which is very useful. The standard 5-point Likert scale can be modified, but generally it ranges from never (0 point) to all the time (4 points). Similar to the CCOS, the CSP consists of four domains. These domains are physical, social, functional and psychological and all carry equal weight. All of these are important to us as individuals for quality-of-life.

The nurse practitioners scanned hundreds of patient assessments and reviewed the literature to initially develop 70 questions. In Phase I, the statistician on the team used a convenient sample of 7 and did an inter-item correlation, which suggested that out of those 70 questions, 13 questions were redundant, essentially asking the same thing in different formats. Phase II involved a convenient sample of 10 patients and our statistician calculated a very high inter-item correlation Cronbach alpha of 0.935. The factor analysis demonstrated the integrity of all questions as having "excellent validity and reliability." In Phase III, a convenient sample of 84 patients was used to verify all previous results, again via inter-item correlation.

Chiari Symptom Profile (CSP) Sample Questions
I have head pain when I cough/sneeze or strain.
I have dizziness or feel faint.
I have trouble swallowing.
I have trouble with my balance while walking.
I have difficulty concentrating, thinking and problem solving.
My symptoms prevent me from participating in activities I enjoy.
I am working shorter or limited hours due to my symptoms.

Figure 2. Sample questions from the Chiari Symptom Profile

The resulting CSP is as follows and is available to anyone who wants to use it at no cost. There are 57 questions spanning four domains (physical, social, functional and psychological) using a five-point Likert scale. The total

scoring ranges from 0 (no disability) to 228 (severe disability). The questions themselves are fairly easy to fill out. Our compliance is high because we do not see the patient unless the form is filled out. They can fill out the form beforehand online, and what is nice about online completion is that the data are automatically stored. Some of the questions are symptom related and others are quality of life. **Figure 2** shows a few examples. Imagine 57 questions that are trying ascertain how the disorder is impacting the patient's day-to-day life.

All statistical analyses were performed using PASW statistics version 18. The overall results revealed Cronbach's alpha of 0.958 ($p < 0.0001$) demonstrating that the survey has strong reliability as a survey tool for Chiari symptoms. This was published in the *Journal of Neuroscience Nursing* in 2013. And I want to stress to the surgeons in the room that when you advocate for your teams, it is going to be the nurse practitioners and your physician assistants that are going to be the primary advocates to get this type of important work done.

There are several reasons to consider the use of CSP or something like it. Of course, we want to understand and quantify self-reported symptoms in the initial evaluation. We want an objective quantitative measure of symptoms before and after decompression. It can also be used as a measure of longitudinal analysis of symptoms and quality-of-life. You can do 5-year studies or even 10-year studies. Then, frankly, as you know your outcomes, that can impact how you treat. Why are the outcomes lower than another group or maybe why are they higher? That should tell us something by looking at the outcomes. Then again, in a similar fashion the use of CSP is to compare outcomes across similar institutions. This is eventually what we want to do if we want to get to a true standard of care in the treatment of Chiari malformation.

There are limitations to our scale. We did not design the CSP to quantify the pre- and post-operative structural and dynamic components of the Chiari I malformation. This was not our goal, but this certainly needs to be part of our future, no doubt, and we will talk about that. Since the CSP was not designed to assess structural and dynamic components of Chiari, it cannot be used to assess those components and inform our understanding of anatomical reasons for changes in quality-of-life. Quality-of-life may improve, but the CSP would not be able to tell me if it improved because I used a certain duraplasty or a certain size of decompression.

Independent Assessments of Chiari Outcome Scales

There have been independent assessments of outcome scales. The senior author on the team that did an external validation of the CCOS is Dr. Limbrick, who is with us today at this meeting.[5] In their other paper, which is a fascinating work, they looked at a number of scales in Chiari I malformation in a systematic review.[6] This was a great effort that included 74 papers which met inclusion criteria. They decided to group the papers into three groups. The first group which included 45 papers indicated that overall symptomatic improvement was based on the Gestalt impression of the clinician after examining the patient. There are 20 papers that have specific signs and symptoms and then calculated outcomes depending on the improvement or lack of improvement. Lastly, another 22 papers did use standardized assessment scales. Of those 22 papers, 6 used disease-specific scales and 11 used general quality-of-life scales. Of the 6 papers using disease-specific scales, only 3 of the scales used had been validated.

Based on the systematic review, the authors' assessment of the CCOS scale was that it is "more reliable than the author's Gestalt impression." However, it "is designed for retrospective chart review and not suited for prospectively measuring patient-defined disease burden before and after treatment." There was also concern that the scale's functionality and non-pain symptoms were found to be less reliable and "may benefit from further definition." That paper also assessed the CSP that was discussed presently. The paper notes, "the recently developed Chiari Symptom Profile has shown strong content validity but has not yet been applied to outcomes research." This is correct. The paper also assessed the CSP, stating that it demonstrates "validity in multiple domains" and serves "as an important aspect of developing a meaningful outcome scale."[6] Since my role is going to be changing pretty soon, one of the key things that I want to do soon is to take our patients at the Medical Center of Aurora— which will certainly constitute a sample well over 500— and try to provide an answer to that first note indicating strong content validity, but lacking application in outcomes research. So, that is our next step: to understand our clinic outcomes, using this tool in our patient population.

I was at the Column of Hope conference in Buffalo this summer where I met Dr. Sumit Thakar from the Sri Sathya Sai Institute of Higher Medical Sciences in Bangalore, India. This hospital only treats vascular neurosurgery and, at least in the Bangalore area, all the patients go to this institution for that condition. They do about 1,500 surgeries each year, though I do not know how many Chiari surgeries they do. Dr. Thakar recommended to the audience at this conference that the CSP be incorporated into outcome measures. Dr. Marcus Stoodley, who directed the conference, also supported that. However, I do not think that you can solely use the CSP.

Future Outcomes Scales

To wrap up, let us talk about the next generation scales. Where do we want to go and where are we going? I think the first of the next generation scales comes from a paper, once again, by Dr. Limbrick and his team at Washington University.[7] The Chiari Severity Index (CSI) looks at both the clinical and the neuroimaging characteristics and that is what I think we need. We clearly need patient quality-of-life measures since we are trying to help the patient. It is all about that, of course. However, we also want to know what we should do and what we should change as surgeons in order to make the patient better. What changes in the neuroanatomy have the ability to change outcomes?

If I had my dream outcome scale, it would include demographics (age, gender, ethnicity, etc.), comprehensive symptom profile including detailed subsections (headache, cerebellar-cognitive affective symptoms, etc.), rare presentations questionnaires (cerebellar fits, paroxysmal rage, etc.), associated conditions, and self-perceived quality-of-life.

The inclusion of the comprehensive symptom profile will be important. We all know that the common presentation includes headache (generally Valsalva-related), dizziness and a number of other symptoms. However, there are cognitive symptoms— the cerebellar-cognitive affective syndrome. In addition to a comprehensive symptom profile, we need to focus on rare presentations. Dr. Limbrick also brought this up in his paper. We need to understand cerebellar fits in children that are related to Chiari. There are two patients with paroxysmal rage that present in the literature. I suspect that there may be more, but we do not know that because this information is hidden until

we start studying it. Other rare presentations may include seventh nerve palsy or hemi-facial spasm related Chiari malformation. I am seeing a young man right now with palatal myoclonus with Chiari malformation and there is only one case in the literature. Obviously, that is extremely rare.

Additionally, any next generation scale will require looking for associated conditions— pseudotumor cerebri, the whole list. The three disorders that I worry about when I see folks are pseudotumor cerebri which is fairly common, CSF hypotension which can be a real detriment to having an operation without first identifying this condition, and craniocervical instability. Of course, there are also a number of other conditions.

Future Directions and Concerns

What else may we need to keep an eye on? Body mass index, hsCRP, Vitamin D and HgA1c are our choices presently. There is no consensus because it has not been discussed. Certainly however, high BMI and hsCRP are clues to pseudotumor cerebri. Vitamin D imbalance can have neurological effects. We assess elevated HgA1c since it indicates a different disorder and you certainly do not want to be surgically treating a prediabetic unless they are being appropriately managed. Fundoscopy and visual field evaluation in the presence of elevated body mass need to be considered, as well as neurological findings (sensory, motor, coordination and autonomic).

Importantly, we need static 3-plane MRI imaging— sagittal, axial and coronal. Chiari is *not* a sagittal disorder. Certainly, for now, that is how we diagnose it using the 5 mm rule on the single, sagittal plane. But Chiari malformation is not only a sagittal disorder. It is a 3-dimensional disorder. We need to quantify deformation of the medulla. There have been tissue strain studies pioneered by Dr. Fraser Henderson. I think in the future we will, hopefully, be able to identify and assess the treatment and outcome of Chiari using 3D imaging. What is the volume of the cisterna magna? What are the complex neuroanatomy relationships? How do the tonsils wrap around? People have "Chiari 0" because they do not have the sagittal herniation, but they have a lateral wraparound of the tonsils around the brainstem and subsequent deformity. We have to begin to analyze the axial views to understand that anatomy.

We also have to define the surgical treatment: The kind of treatment that is being utilized and the amount of bony suboccipital decompression. There is a general consensus currently for longitudinal decompression dimensions— approximately 2.5 cm to 3 cm, very rarely 4 cm. The transverse amount of compression is the key measurement for the foramen magnum. In very large decompressions (up to 7 cm), we have to have the skin closed or else the patient may have a blowout. In not doing this, we are ignoring the spinal tension band that keeps our head in balance. When you see folks that have had these decompressions and all they have is skin above the water pocket, you can press on it and subsequently pressurize it. That space needs to be rebuilt. Some of the plates that we use have to be specially designed to be able to reconstruct and pull that muscle, recreating the tension band. Of course, I have some strong opinions on that issue, in particular.

There are other surgical considerations that still require consensus, as well. For instance, epidural decompression versus duraplasty. Also, if the epidural is bone-only, defining what materials are being used or how to test the duraplasty. All of these need to be recorded in the literature. We need to find out which treatments work the best. We need to be more detailed in

defining the tonsillar morphology and its laterality. Is there tonsillar pointing, fibrosis, or cystic degeneration of the tips of the tonsils? What about this lateral medullary compression, or the 11th nerve pathology with the beading of the nerve from chronic compression? That has been defined but maybe not discussed a lot. Again, also the fibrosis and the cystic degeneration of the tonsillar tip should be recorded. We need a way to assess medullary elongation. Intraoperative ultrasonography can be used to see what is happening. In some patients we certainly see tonsillar pistoning. I have seen the occasional what I call "trampolining," wherein the piston-like movement causes the cervical cord to "bounce" in a movement mimicking a trampoline. Then, of course, the extent of the longitudinal medullary and tonsillar tissue movement. In some cases, we can actually see the medulla pulsing. That should be able to be characterized. And, finally, in the future, should we have 3D cine MRI studies to tell us more about the hydrodynamics and how important those physics are and whether or not they correlate with outcomes.

Conclusion

In conclusion, a Chiari-specific outcome instrument that measures symptoms, quality of life, surgical steps and radiological outcome would facilitate comparison of outcomes across institutions and reduce the disparity in the surgical techniques currently utilized. Thank you.

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7.

Study Update: Posterior Fossa Decompression with and without Duraplasty

DAVID D. LIMBRICK, M.D., PH.D.

Introduction

Before I get started, I want to just make a few comments. First of all, thank you, Dr. Oró for discussing those research efforts that we have put forth. I kept waiting for the "but," and it never came. So, that is what I really want to thank you for— not pointing out all the flaws in our papers. Secondly, I wanted to just comment that I have already learned so much this morning. This is such a great group and all the talks have been so informative. I know we generally think of this as a research conference, but I know I learn so much about things that might even modify my practice from all of you, so I appreciate that.

Each year at this meeting, I try to give a update about our posterior fossa decompression (PFD) trial. In this update, I can announce that we finished enrollment and have almost finished outcome collection for the trial. I will not be able to share any of the results because I am blinded and even though our clinical trial coordinator, Thanda Meehan, is not blinded and is with us today, she will not be allowed to share them because she is forbidden. Thanda has done a lot of the heavy lifting in the administration of the trial in partnership, actually, with Bobby Jones CSF. I will talk a little about that going forward.

Background

This surely doesn't need introduction in this group, but I will quickly review the background and rationale for this trial. As we all know, one of the most controversial aspects to the treatment of Chiari with or without syringomyelia is whether or not to perform an extradural posterior fossa decompression (PFD), versus adding duraplasty (PFDD). Again, I won't spend any time going through what this means, but when you look back at our data about how we address this question, it seems to have been discussed in the neurosurgical field for more than 20 years. Just as evidence of this, there was a meta-analysis in the *Journal of Neurosurgery Pediatrics* published 12 years ago which references data from 10 years before that.[1] So, this is something that we've been thinking about for a long time. Another meta-analysis[2] was published in 2017 with the same findings— and this is even 10 years after that initial meta-analysis. Our knowledge up to this point does seem to indicate that duraplasty may be associated with higher rates of complications and a lot of those are related to CSF hydrodynamics. When this methodology is chosen, also, it takes longer to do the actual surgery. On the other hand, however, it may be more effective and we do not have data to confirm which procedure, if any, is preferable. So, that is essentially the question really at the root of the study that I'm going to talk about. Editorials and literature reviews in the past few years have described the root of the problem: that the data underlying this issue are not high-quality, and therefore, we need to do a prospective randomized control trial (RCT) to get an answer to this question.[3,4]

Back in 2011, we started a multi-institutional platform that we call the Park-Reeves Syringomyelia Research Consortium. We were able to do this through the generous donation of the Reeves Family. We created this multi-institutional group, consisting of multiple specialties

including neurosurgeons, orthopedic spine surgeons and inpatient advocates. The goal was to collect data on one thousand patients. At the time we weren't thinking about doing a randomized control trial, just a registry. We started with just five centers and it sort of grew organically over the years, mainly because people began to express interest in being involved. Over time, it grew to 42 centers, and that is where we are at right now.

The PFD Trial

As we got more and more preliminary data and we built the infrastructure and investigators became quite committed to it, we went ahead and applied for grants in order to address this question about duraplasty. Our application and the concept and rationale were endorsed by the major neurosurgical organizations. They read the grant and the data elements before we submitted it. We also partnered with Bobby Jones CSF, which was really important for the Patient-Centered Outcomes Research Institute (PCORI).

Essentially, there are two types of RCT series that we could have chosen. The first is the type of RCT where you roll the patient back into the operating room and you flip a (usually electronic) coin. We did not choose that option and there a lot of reasons for that decision. Instead, however, but we chose to structure this study as a "cluster RCT". This means we randomized procedures by site, rather than by patient. Specific sites for the entire cohort were randomized to either doing duraplasty or extradural. We had training videos, parameters on the operations, and so forth to ensure standardization of the duraplasty and extradural methodology.

As many of you know, surgeons feel quite passionately that they already know the best answer. This caused some difficulty in the beginning of the trial. At times, investigators were not necessarily delighted at their randomization if they were allocated to the extradural group and they were strong duraplasty supporters, or vice versa. That was something that we did have to work through and, fortunately, we were able to get through it. A major goal of this trial, of course, was really to help with a paradigm shift away from what we're currently doing—single center surgeon preferences and experiences— and to try and think about this PFD and PFDD conundrum in a more global sense. We want to not just optimize the care of one patient at one particular center, but to all patients being seen by all surgeons, particularly new surgeons as they begin their training. So, this study is really an investment in the treatment of children, going forward.

We had three aims. The first aim was to determine whether the extradural PFD is associated with fewer surgical complications than PFDD. PCORI was most interested in this in their request for application. Of course, our hypothesis was that PFD would be associated with fewer surgical complications. We looked at many different complications at different time intervals. Some of these complications that we assessed included CSF leak, pseudomeningocele, aseptic meningitis, infection, hydrocephalus and the requirement of certain additional surgeries. The second aim was to determine if the extradural operation provided non-inferior clinical improvement in syrinx regression compared to the duraplasty operation. The level of evidence and statistical sophistication in superiority equivalence in non-inferiority is variable. This has to do with the design of the given trial and the statistical complexity is beyond what I want to get into today but, essentially, studying this PFD question in terms of non-inferiority makes the trial aim achievable. Lastly, the third aim specifically looked at quality-of-life: is PFD associated with a superior

quality-of-life compared to PFDD? I will circle back on all this because of Dr. Oró's really wonderful talk earlier.

Participant Enrollment

We knew at the outset that enrollment criteria would be controversial. The first criterion was simple. Since this would be a pediatric study, we would offer enrollment to patients less than or equal to 21 years of age. The criterion that identified "Chiari malformation" was, unsurprisingly, controversial. We started by setting this criterion across investigators and then revised it using a Delphi method. Now, you can certainly argue whether 5 mm is the right or wrong cutoff but we didn't want to get into that theoretical question. Rather, we wanted to be in a category where neurosurgeons across the network would uniformly agree that the patient being enrolled into the study definitively had a Chiari malformation. Thus, we chose 5 mm of tonsillar ectopia for the categorization of Chiari in the study. Finally, syrinx size. We wanted to be careful not to include that any T2 signal abnormalities that would be considered a dilated central canal. To ensure this would not occur, we set a syrinx diameter minimum of 3 mm and maximum of 10 mm. We set the maximum at 10 mm, because the pool of investigators felt that if the patient had a syrinx beyond 10 mm in diameter, there would not be appropriate equipoise in offering an extradural-only procedure to that patient. The exclusion criteria were much more straightforward. Exclusion criteria included: a syrinx ≥10 mm, basilar invagination and clival canal angle <120º on neuroimaging, prior decompression surgery and individual patient unwillingness to participate in the study.

Outcomes Measurement

Particularly because the PFD trial is funded through PCORI, we were very careful in our consideration of quality-of-life measures we would select to monitor participants in the trial. I've been fortunate to surround myself with great people over the years and a lot of the work we have done assessing quality-of-life tools has been made possible through the efforts of people like Dr. Jacob Greenberg, with whom we published the systematic review that Dr. Oró introduced earlier.[5] From this work, we realized just how much we need to move away from Gestalt impression, especially as a surgical outcome. **(Figure 1)** Instead, we need to shift our focus on using more disease-specific quality-of-life instruments.

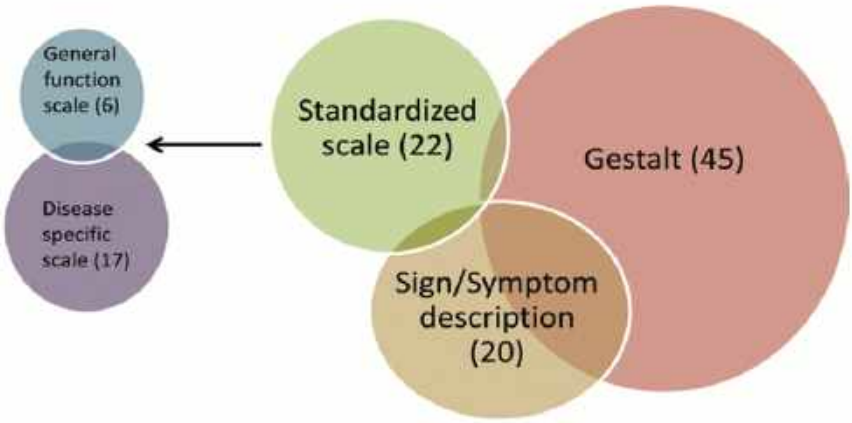

Figure 1. Greenberg J., et al. *J Neurosurg.* 2015.

Our close collaborators at Vanderbilt, Dr. Wellons and Dr. Shannon, developed what they call the "CHIP," or the Chiari Health Index in Pediatrics.[6] It is validated both for parent report or patient report and it can be administered to patients

above the age of five. This is not dissimilar to Dr. Frim's scale, the Chicago Chiari Outcome Scale, in that it also surveys pain and non-pain kind of symptoms. It essentially allows a composite index of health-related quality-of-life. Finally, we also used the CSI scale Dr. Greenberg developed to stratify our patients for this trial.[7]

Study Timeline and Engagement

The trial is scripted in a significant way. The Park-Reeves database is relatively thorough, as many of those in the audience already know. The trial, however, is scripted such that we interrogate and query the various data points at the relevant timepoints— prior to surgery, less than 1-month follow-up, 3 to 6-month follow-up, and then at 12-month follow-up. We collect clinical data, radiological data and then quality-of-life data, both with the CHIP and also with a generic health-related quality of life index called the Health Utilities Index Mark 3 (HUI3)[8] which has also been validated in children.

Again, I am fortunate to have surrounded myself with excellent people because when we first started this trial, we had lots of enthusiasm from the investigators in the neurosurgical community. It turns out, however, that this is not where you need the enthusiasm for this type of trial. You need it from the patients to be able to contribute. It turned out that there was a little bit of noise online indicating that our patients themselves were not as enthusiastic about participating. This was something that Bobby Jones CSF really helped us through by being supportive of the trial and helping us to reassure patients that this is an important research question. In a way, it may be the most important in that the opinion of a single surgeon is very valuable but the data that helps to form that opinion is perhaps just as valuable. So again, I can't thank Bobby Jones CSF enough. They helped not just by posting about it through their social media sites, but also providing brochures that were handed out to the various site clinics. If a patient was being offered participation, the brochures were included in an information packet in patient-friendly language and had the endorsement of Bobby Jones CSF. It was very helpful.

PCORI also really strongly favors involving patients and the patient community in the trial. Written into the grant was funding to help support these efforts. One of them was a St. Louis chapter of Bobby Jones CSF and we do an event one to two times a year. Actually, everybody you see from Bobby Jones CSF here in this room comes to St. Louis and helps us to run a community advisory panel. The video presentations are then posted online. And again, it's just a really great partnership.

The engagement activities for this trial extend beyond our local patient chapter, however. We give frequent reports at meetings of various advocacy organizations and advisory panels, including, for instance, Bobby Jones CSF and the Community Advisory Board at Vanderbilt University. We've given reports at the PCORI annual meeting in Bethesda. Then, of course, we often report at many of the pediatric neurosurgery meetings because they are attended by many of our clinical stakeholders.

Participant Demographics and Retention

Our initial enrollment target was 148 participants. We screened 998 patients and excluded the vast majority, based almost entirely on syrinx size and in many cases tonsillar position. We offered enrollment and successfully enrolled 163 patients. So, we actually exceeded our target enrollment. In the end, we enrolled 161 participants who ultimately had surgery which is an amazing feat.

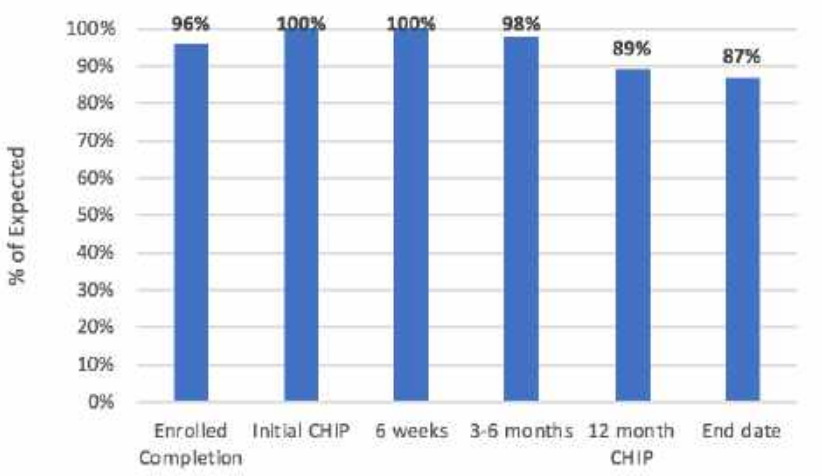

Figure 2. PFD Trial enrollment and retention rates.

We are actually coming up on the last bit of data collection for the one-year time point. As of right now, we see a female preponderance and a vast non-Hispanic white preponderance. The average age of participants is about 10-years-old and the radiological parameters that we measured all seemed to fit within the distributions that we would expect in this patient population. Not surprisingly the most common symptom was headache, occurring in more than half of the participants we enrolled. Importantly, we did collect some more granular information in terms of where those headaches were localized, how they would present and so forth. A majority of the data I will describe today are from the Data and Safety Monitoring Board (DSMB); I will not have access to a lot of the nitty gritty data until the study's conclusion.

Typically in clinical trials, there is a huge drop-off in retention after initial enrollment. Very impressively—and I thank Thanda for this— we were able to retain a majority of participants, throughout the trial. **Figure 2** illustrates that as of the six-month time point we are at 98% retention of participants, which is unheard of. Then for the 12-month time point, you can see we are at 89%. We are not quite at that 12-month time point for everyone, so we expect that to increase too. Again, I really do have to acknowledge Thanda who has been on this on a daily or weekly basis and because of that, we have a really unprecedented follow-up. I think part of that excellent retention rate, however, is also related to the strength of the relationship between a physician and the patient in the setting of this particular condition.

The study follow-up will be completed in about two months and the data will be available, as we will be reporting it soon. There is a phase in the PCORI grant-making process called "peer review"— not manuscript peer review, which will be a separate process— where PCORI will take our data that we have generated, and evaluate the statistics and the findings before it can be submitted for publication. That will be an approximate six-month period. We plan to start this shortly, but we won't actually be submitting for publication until after that is completed.

Complications & Summary of PFD Trial Review

Just a few things: I did manage to get some data on complications from the DSMB meeting, so I just wanted to show a few things. Intra-operative complications, not surprisingly, were extremely rare. The other complications we saw were very much in line with what we would expect given what is currently in the literature: CSF leak, pseudomeningocele, chemical meningitis, infection, et cetera. Only small percentage of patients in the entire study in either arm of the trial experienced any complications at all. We also noted that it was relatively uncommon to need additional surgical treatments, even in the setting of subsequent CSF disorder, as Dr. Jackson was telling us earlier.

So, to review, enrollment is complete. Importantly, all the demographics, baseline characteristics, medical history and anatomical factors were in line with what we predicted during the design of the study. The complication rates were low and consistent with pre-study design. We have high agreement with the expected exams in terms of follow-up. So, it seems like everything is on track and, again, a great team has really been tremendously helpful in this.

Additional Research Avenues

I just wanted to take an extra minute or two to talk about the other work that we are doing now with genetics. This is not through Park-Reeves per se, but many contributors are involved in both efforts. This is through a multi-center collaborative group including Washington University, University of Utah— Dr. Brockmeyer has been invaluable in these efforts, Stanford University, Duke University— Dr. Ashley-Koch sent us DNA from some of her patients, Vanderbilt University, Ohio State/Nationwide Children's, Toronto/Sick Kids, Arkansas, Johns Hopkins, Cincinnati and Indiana/Riley.

We've been doing some whole exome sequencing on patients. Our goal is to sequence one thousand patients. We have done over five hundred, to date. We are working with Dr. Ashley-Koch, Dr. Brockmeyer and other groups to identify and investigate copy number variants, rare variants, new mutations and other genetic factors that may be implicated in hypermobility.

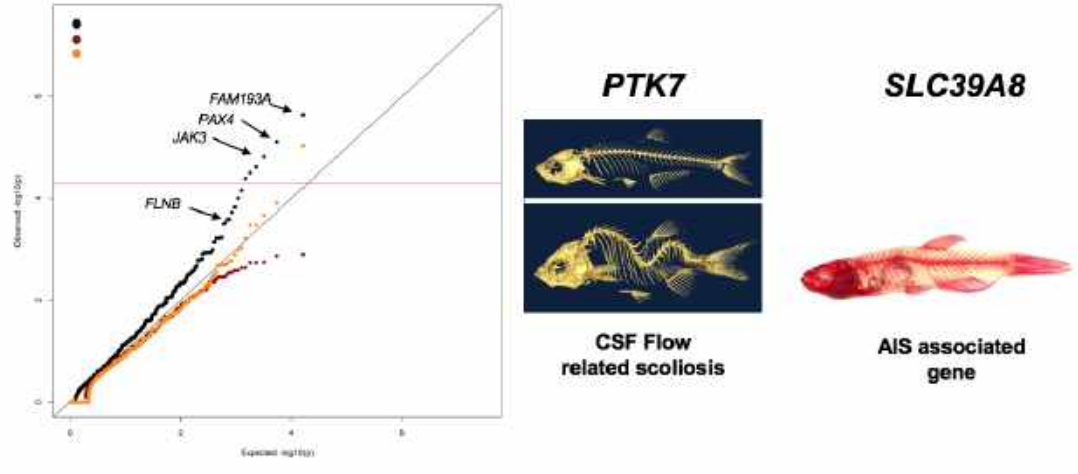

Figure 3. QQ plot summarizing candidate genes that may be implicated in Chiari malformation and related disorders.

We funded this initially through a pilot grant from the Missouri Spinal Cord Injury Research Program and we are making great progress. We have a small collaborative group within Washington University that is working on this and it includes myself, Dr. Christina Gurnett, and Dr. Gabriel Haller. The group is open to anyone else who would like to contribute. It does not have to be syringomyelia, it can be Chiari alone. It does not have to be a pediatrics case; it can be an adult. We are interested in augmenting the numbers to get to a thousand.

Unlike what we heard earlier from Dr. Ashley-Koch, our group is taking a little bit less of a targeted approach looking at exomes. We have identified a cohort of genes, some of which are illustrated in **Figure 3**. Dr. Haller works in our department and is a scientist geneticist, not a clinical human geneticist. He is currently developing a CRISPR model in zebra fish. He also has an *in-vitro* assay to look at the functional impact of each gene mutation. What you see here, this fish with scoliosis, is actually one of his recent publications in adolescent idiopathic scoliosis using the same design of broad human sequencing, identifying candidate genes, evaluating them *in vitro* for functional importance and then putting them into a CRISPR model. We have mice and zebra fish, but the zebra fish are so much more amenable to quick turnarounds in development and assessment. That is what we are doing right now. I appreciate everyone's attention today.

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Artificial Intelligence for Real-Time, Automated Cerebral Ventricular Evaluation

KRISTEN YEOM, M.D.

Introduction

I would like to thank the Bobby Jones CSF for inviting me. Today I represent myself and my partner-in-crime at Stanford, Dr. Gerald Grant. We have been interested in looking at the ventricles, looking at Chiari, and looking at radiology in a way that is more clinically useful to the neurosurgeons who are frequently treating CSF disorders. We believe that we are a team and we can do better than before, especially with all the advances that are happening in medicine every day. These advances stretch from the realm of technical developments to the modern-day ways of machine learning-based analyses.

What is "Fast MRI"?

At the last Bobby Jones CSF Think Tank in San Diego, we discussed how we have come quite far with imaging. As discussed at that meeting, "fast MRI," or "fast scans" are actually getting quite good. This modality has become quite useful, not just in looking at hydrocephalus, but also in routine trauma follow-up, cysts, and a lot of other things.

Dr. Grant and I have been using these fast MRIs for Chiari patients, as well.[1] This all started because we wanted to make it more amenable for our pediatric patients to get scans without having to wait a long time, get contrast, or undergo sedation. A lot of these, in and of themselves, carry risks of their own, so we wanted to find a way to make these scans easier and faster for these patients.

We have uncovered through this work that fast MRI can be quite useful for looking at a lot of the anatomical details. We are able to look at the syrinx size to an extent that is fairly comparable in a sense, as you can see in **Figure 1**. Additionally, the routine T2 image is not always inherently superior. You can see that there are a lot of CSF flow-related artifacts that can hamper image details.

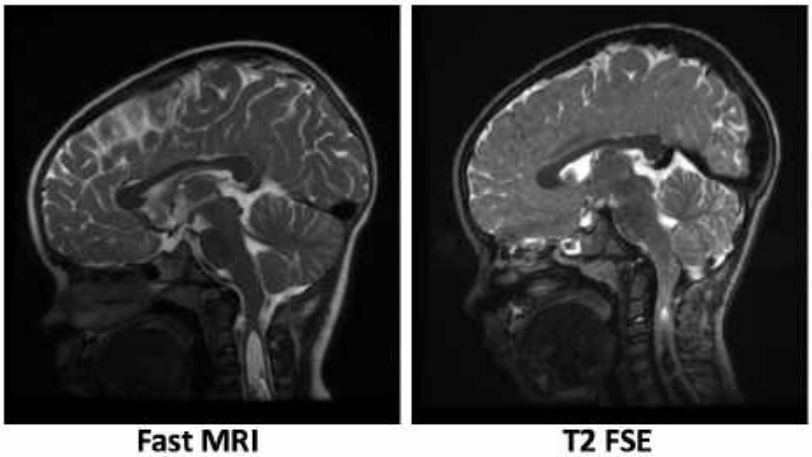

Figure 1. Five-year-old female, post-decompression follow-up. Syrinx is well-visualized on fast MR; more CSF flow artifact on TS FSE.

I have shown some of these slides before at these meetings. In this T2 image (**Fig. 2**), you can see that there are a several artifacts that obscure the cranio-cervical junction, although, of course, in the fast MRI, there is less contrast and image quality. There is general SNR or signal to noise that you can see with the routine fast scan.

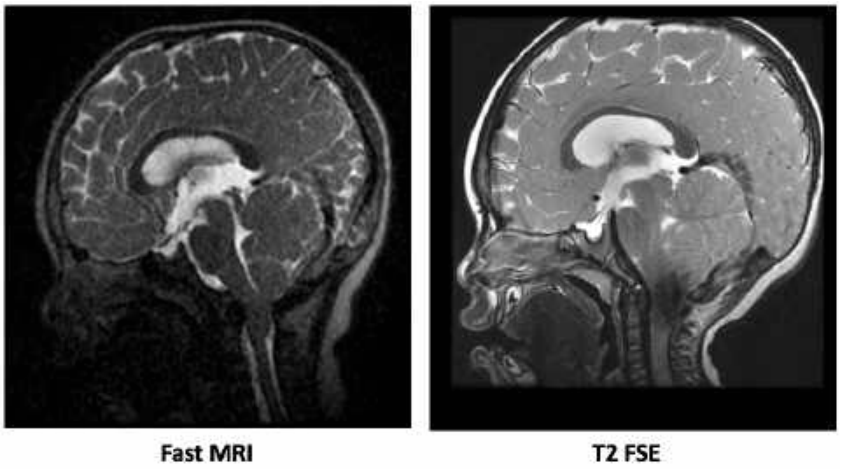

Figure 2. Three-year-old, Crouzon syndrome, shunted HCP, mild low-lying tonsils not requiring surgery. Fast MRI obtained to follow-up shunt, ventricles, and tonsils.

We are experimenting with things to improve the image quality of these scans, especially for brain details. **(Figure 3)** There are fast scans to the left and right that now have even more image detail. You can now see the gray and white matter at a faster time— 50% faster. The average time for TR on SSFSEx is 550 ms, so a lot faster.

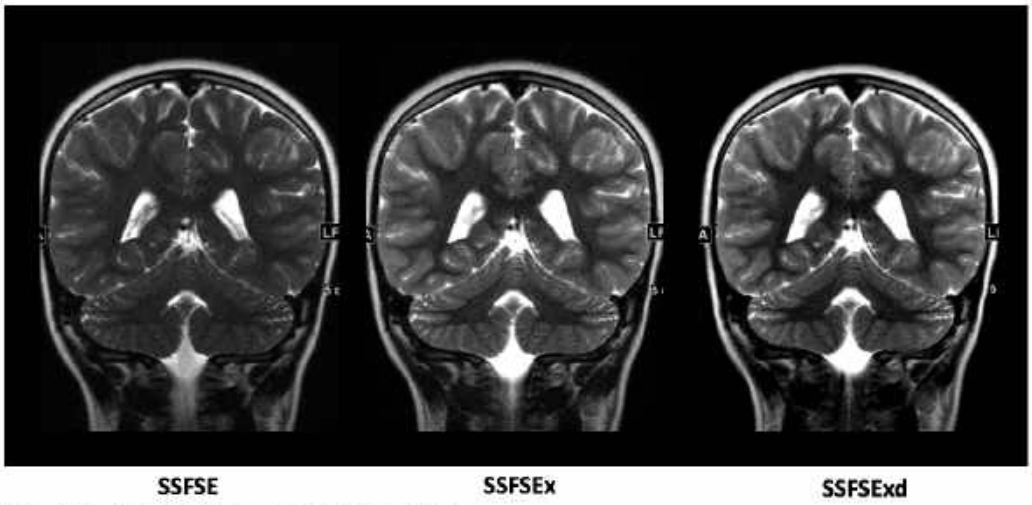

Figure 3. Fast scan improvements over time.

I also want to point out that we are now trying to use this modality for syrinx assessment— "fast spine," as we are calling it. This work will hopefully enable us to use these scans for both the brain and spine in our patients.

Artificial Intelligence & its Application to Neuroradiology

Going forward, I want to show you that we have really come quite far since the old days when we had to look at midline shift and pneumoencephalogram. We offer all these multimodal approaches. Not only do we have brain scans, but we also have ways to observe flow, assess a syrinx, identify complications of surgery, hydrocephalus, shunt failure, et cetera.

I showed a video last time showing how we are trying to implement this dynamic imaging because I think that we can do better. It had been a two-minute T2 dynamic weighted image— nothing fancy. It does require a little bit of up-front post-processing, but again, what we really want to see going forward is a more dynamic way to assess, process and look at that pulsatility or "pistoning". That is hopefully where we want to go in the future.

But, now what? Where do we go from here? What can we in the radiology discipline bring to our neurosurgeons to really help our patients more? These new applications may be quantitative. They may involve biomechanics, or looking at motion. Maybe we refine how we look at microstructures, whether by using diffusion tensor imaging, or even shape analysis of microfiber bundles. These are all things possible.

Every day, you turn on the news and you hear about artificial intelligence (AI); it is really everywhere. AI helps us with our scheduling; it helps us find out what movies to watch. I live around here in the Bay Area and we even have self-driving cars. So, AI is already fairly ubiquitous and the question now is, *How do we leverage all of this and bring it to our neurosurgical patients?*

There are many things that we can do: object detection, anomaly detection, localization, segmentation, classification, regression tasks— these are all things that are possible through the use of AI. Of course, folks talk about "deep fakes" and other uses of AI which are really a security concern, cybersecurity and politics— things like that. But there are ways to retool some of these "bad" advances in computational methods and techniques for better utilization in medicine and to better help patients.

Of course, more of us are understanding how we can best apply these advancements in medicine. Certainly, we are getting better. A lot of this advancement has to do with theories that have been present for a very long time. We can trace some of these ideas back to the 1800s, back to Gauss. The way that we do statistics and analysis of data has been around. Even what we call AI, or the "neural network," has been around since the 1990s. The one big thing that has really changed since the 1990s is that we have faster computers now. The new processing units have made this shift possible. We no longer have to wait for years for some kind of prediction of something to happen. Now that we have these fast computers, we can do a lot of different things. You can see that AI is doing a much better job with each passing day in the computer science literature. They're even doing a much better job distinguishing parrots from guacamole and muffins from dogs! **(Figure 4)** These are papers that actually exist out there. They are awesome and so creative about how they approach these problems.

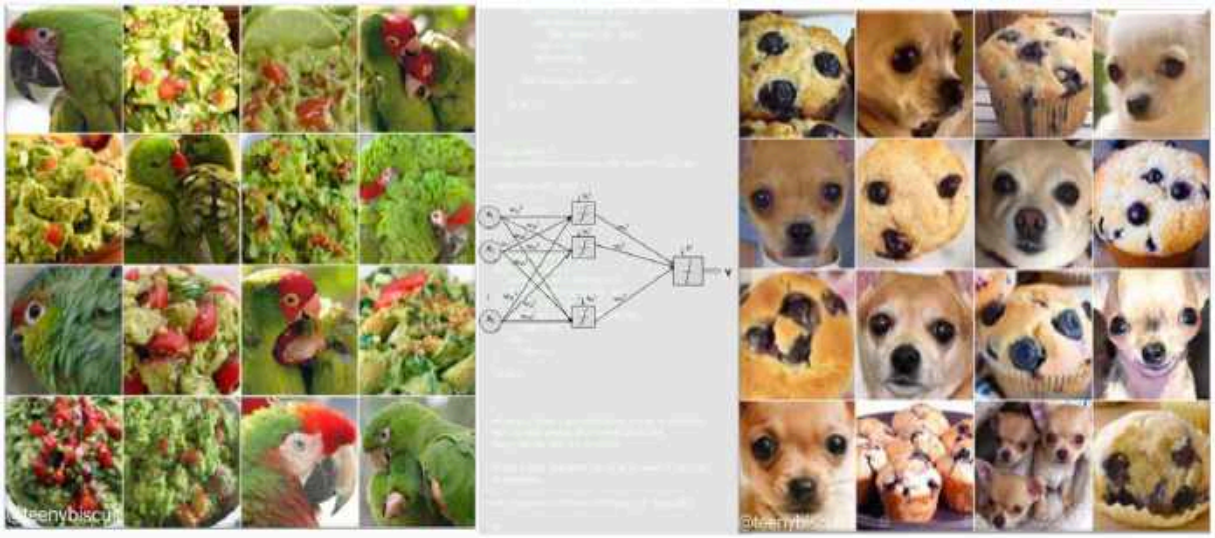

Figure 4. AI learning to distinguish parrots from guacamole and muffins from dogs.

But then, as clinicians, we have to look at these problems and determine how we can use them as tools to benefit our patients. You bring these methods into the medical domain and it becomes less about differentiating between dogs a muffins, and more about differentiating between a bleed versus no bleed on MR imaging. I am sure you are aware that these papers already exist in the medical literature. So, yes, we can train AI to accurately identify a bleed on a scan. The success or failure of these programs has to do with inputting data with labels into the algorithm and appropriately training so-called "computer vision". Using labeled data, we can use a neural network to train the model. If the model does a bad job of accurately identifying the data you are training it to find, you penalize the model and make it go back and re-learn its task until you get to a point where you are satisfied that it is accurate. Certainly, we can debate what it means to be "satisfied" with the model, but that is a separate topic. In essence, however, it can be done.

Before I get into some examples of what is currently available in the literature, I wanted to present some sobering facts that even I did not know until I looked it up. Twenty million radiology reports contain clinically significant errors and diagnostic errors play a role in up to 10% of patient's deaths.[2,3] Even more concerning is that ⅔ of the world population lacks adequate access to radiology specialists.[4,5] This is because many hospitals have radiologists looking at imaging, but some of those radiologists may not be as comfortable looking at neurological scans. A radiologist may be a superstar at reading mammograms, but if he has to look at a neurological scan because he happens to be on call, he might not even be familiar with Chiari, let alone may he be able to accurately read it on a scan.

Knowing these facts, the question becomes how can we empower modern radiologists and neurosurgeons using the massive amounts of data at our disposal? I see many multicenter trials occurring. We have retrospective and prospective data. There is an unbelievable amount of data already out there, so how can we leverage these existing datasets to learn more? There are data that are useful, not only in radiology, but also in patient symptoms, laboratory data measurements, headache profiles, et cetera. We want to use all of that information to try and create a predictive model for surgical failure, patient outcome or other outcomes that might be identified. I think there are many ways that we can collaborate and work together towards this effort. Chilamkurthy and

colleagues have published on how this may look, going forward.[6] Overall, this is interesting because you can train a neural network to accurately distinguish a dog from a cat, identify whether there is or is not blood on a scan, but a lot of this work has been done in adults.

In the end, this is all about data— and massive amounts of data. Computer scientists are able to teach AI different recognition tasks because they have millions of data points available and the computer has the ability to scale those numbers even more. With medical data, this ability suffers slightly because some conditions simply do not have that much data available to scale. For instance, there is probably plenty of data available if we are talking about adult head CT images, but if we are talking about Chiari, the data are more scarce. Therefore, developing an algorithm for Chiari may require a little bit more supervision of the AI. Of course, there are ways to deal with smaller amounts of data. In some of these cases, you may not even need clean labels. It is possible that the model can learn by itself. Just as you would teach a kid how to ride a bike, you can teach the computer how it may decide to approach a particular issue.

Practical Applications: Improving Image Quality

So, again at Stanford, we have been looking into how we can apply these advancements in Chiari and similar disorders.[1] We played with a smaller data set consisting of about 1,000 head CT scans. We decided to see if the AI would be able to predictably identify a fracture. Thus far, we have seen somewhat promising results. Then using only sagittal images, we compared the AI's performance to one of my neuroradiology fellows and it performed almost as well as the fellow. Maybe if we add on axial data, it will do better.

A lot of time when we discuss computer science, we hear the term "black box", by which people mean that the computer figured it out, but we do not know what it did to draw the right conclusion. In a way, this is true; but there are ways to see and do some quality control. We can actually generate heat maps **(Fig. 5)** and see what features were most important within the image space to make the prediction. In this case, it looks sort of appropriate. There was a focus in the area of the fracture and not looking at something like the skull or another place that would be totally off.

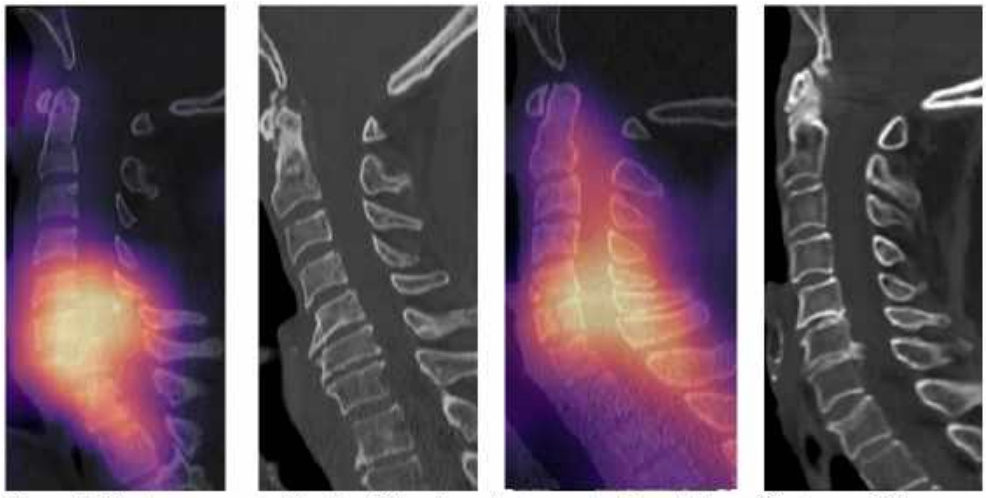

Figure 5. Heat map generated by identifying important areas to AI prediction of fracture on CT scan

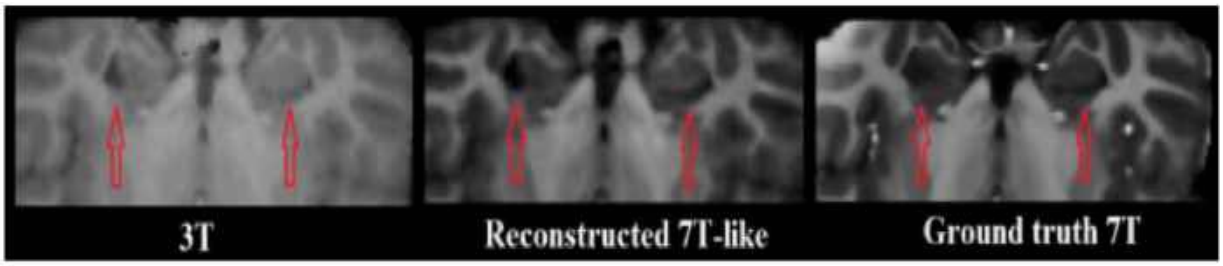

Figure 6. Model-constructed 7T-like image generated from 3T and ground truth image

The next concept is similar to that of the "deep-fakes" we spoke about earlier. If you have some paired image data, the model can actually create another image that is almost new. If you pair a 3T resolution image with a ground truth image (7T), the model can learn to generate brand new data that looks just like 7 Tesla resolutions.[8] Essentially, the model can make the image prettier. You can even transform images from one modality or sequence to another. If you have T1 and T2, you can train a model to take a T1 image and generate a T2, even if it had never seen it before.[9] So, even in medicine, you can do these weird things that are similar to the processes of developing deep-fakes.

With these tools, we have the ability to significantly improve image quality, while also reducing the burden on our patients, particularly in pediatrics. If I have my "fast scan" and my pretty T2 scan— the fast scan occurring within a few seconds, and the T2 within a 4-5 minute sequence— can we train a model to take a fast scan, but generate a T2-like image quality? Of course, this is feasible. It comes down to time, effort and the willingness to do make it happen.

We recently published on whether a model could potentially take on some of the more labor-intensive tasks of radiologists. **(Figure 7)** We gave the model a segmentation task and we overlayed the model's predictions on top of the full DICOM brain MRI. **Figure 8** shows what the model's prediction looks like on the patient MRI, moving with each viewed slice of the MR image.

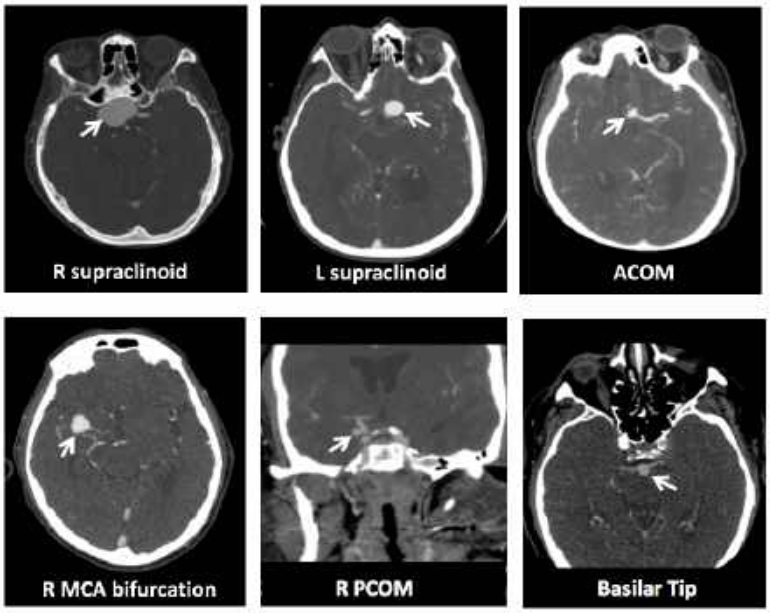

Figure 7. Labor-intensive radiology tasks

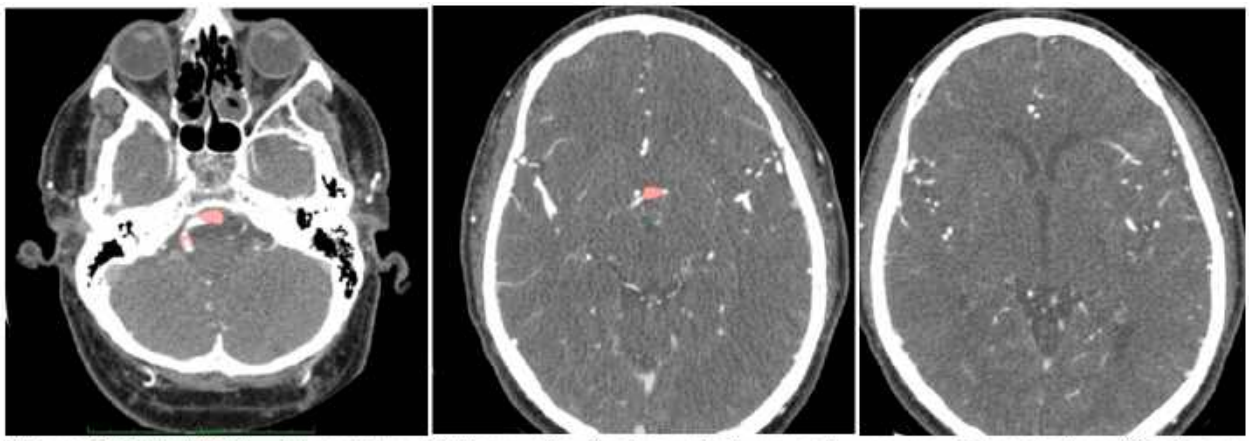

Figure 8. Patient MRI with model prediction overlay (red); predictive overlay moves with each slice of the image

The idea was to treat the MRI on the viewing station as if it were a movie. Medical images are not always static, you can move in and out of the anatomy. In this way, you can think of it like a movie. We pre-trained the model with YouTube videos to teach it how to recognize that dynamic state.

Practical Application: Automated Segmentation

For a lot of these disorders that do not have the massive amounts of data required for quantitative modeling, there are other avenues. Perhaps a more qualitative approach will be required in our assessment of the cranio-cervical junction, Chiari and tonsillar descent, whether it is a degree of biomechanical motion, the quantitative extent of deformation, et cetera.

We started some of this work by looking at the ventricles because we had a lot of data. This was a project done in partnership with Sick Kids in Toronto, Stanford, Dayton Children's and others. We contributed a lot of data with a goal of automating ventricular segmentation and volume predictions. We wanted the model to segment the ventricles in categories, whether they were big, small, crooked, et cetera— because it does get tricky. We thought it would be really nice if we could train a model to identify where the ventricles are, segment them on its own, and then tell us the volume of the ventricles. If it were possible, it would make my life as a radiologist easier and it may make the neurosurgeons' lives a little easier, too. Maybe it would not make a difference in the end, but then again, maybe it would. Nevertheless, it is more quantitative than the applications discussed before, so we went ahead with the project.

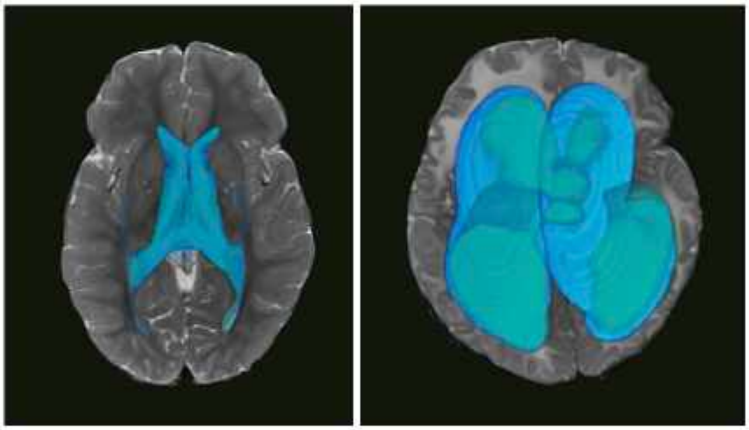

Figure 9a. Normal

Figure 9b. Hydrocephalus

We took examples of our human segmentation and trained our network to predict it. Once it learns how to segment it, the model can blow it back up into image space and provide a nice visual. In **Fig. 9a**, we see what the model produced for a

normal patient. Interestingly, the model figured out not to include edema that was present on the scan near the ventricle, which was kind of nice to see. In a patient with hydrocephalus, there was, in fact, a lot of white matter and edema on the scan but again, the model effectively learned to ignore that, which was also quite nice. **(Figure 9b)** We used about 400 data sets to train our model and it has performed relatively well.

Now, you might say, *Well, automatic segmentation tools already exist*. And to that, I would say, yes and no. The tools that exist already are not truly automatic. You can input this T2 and it will give you an output within 0.03 seconds—that is how fast neural networks run these days. You put an input and it gives you an output, almost instantly. Some of the traditional software and tools might take 7, or even 10, hours. Additionally, you generally need to manipulate your image data in a nifty file format, which none of us really have time to do. Very often, in order to make these tools work, you have to hire a neuroscientist who knows how to image manipulate, put the image into an image common space and then use a software. And even once you use the software, you will generally need to know some basic software skills, such as Matlab. So, in actuality, it really takes a lot of time. Additionally, we decided to run some of our pediatric patients through those other tools and because the models and software that are available are mostly built for adult patients, the pediatric images fail. We have had many failures through that process because it will not intake based on the different size.

Figure 10 shows an example where the green is a human segmentation and the purple is what a software tried out. This took 7 hours to complete, and it failed. It probably failed because it is not used to looking at a pediatric scale. To give it a second chance, we also fed it a scan with a very large ventricle to see if it would perform better and the results were mixed. Our model, however, learned and was able to accurately predict the segmentation on the latter image.

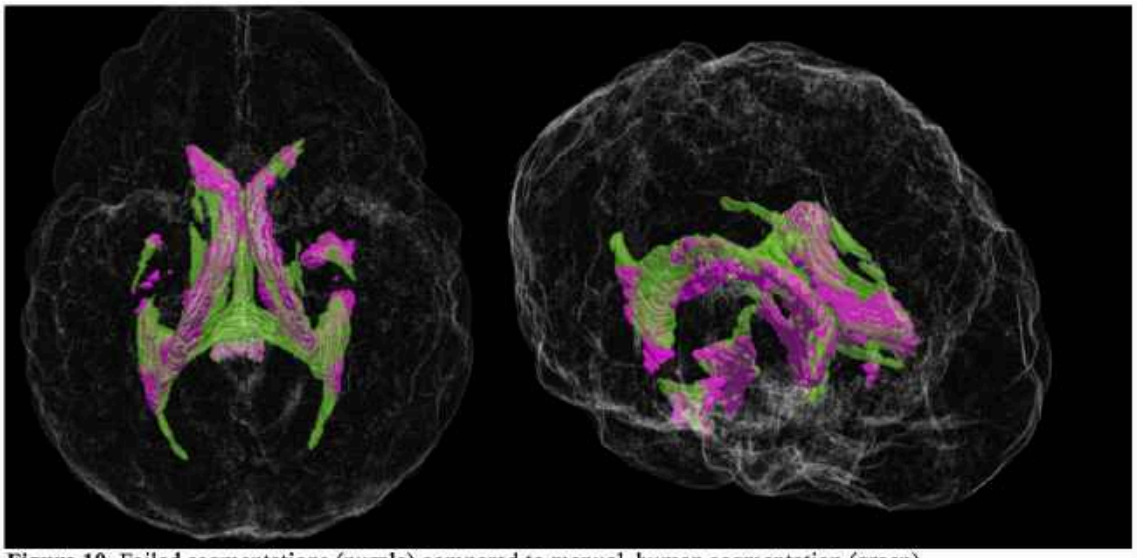

Figure 10. Failed segmentations (purple) compared to manual, human segmentation (green)

Practical Application: Neurosurgical Applications

In addition to assisting neuroradiology and diagnostics, there are possible new applications in neurosurgical navigation. Currently, most intra-operative navigation systems are 2D guidance systems that require manual segmentation. But can a model segment tumors for us? Can we integrate it into our operating system? Can we segment the vessels so that we can look at the vessels that supply the eloquent area in relation to the tumor, in a 3D space? This would save us from segmenting these areas ourselves intraoperatively.

And, yes, we are getting there. **Figure 11** shows a nice example. This is not yet published; we are trying to get it out in the next couple of months. We compared human segmentation, the trained model, and again, we see promising signs that it can do it. The more data we collect, the better the model will get.

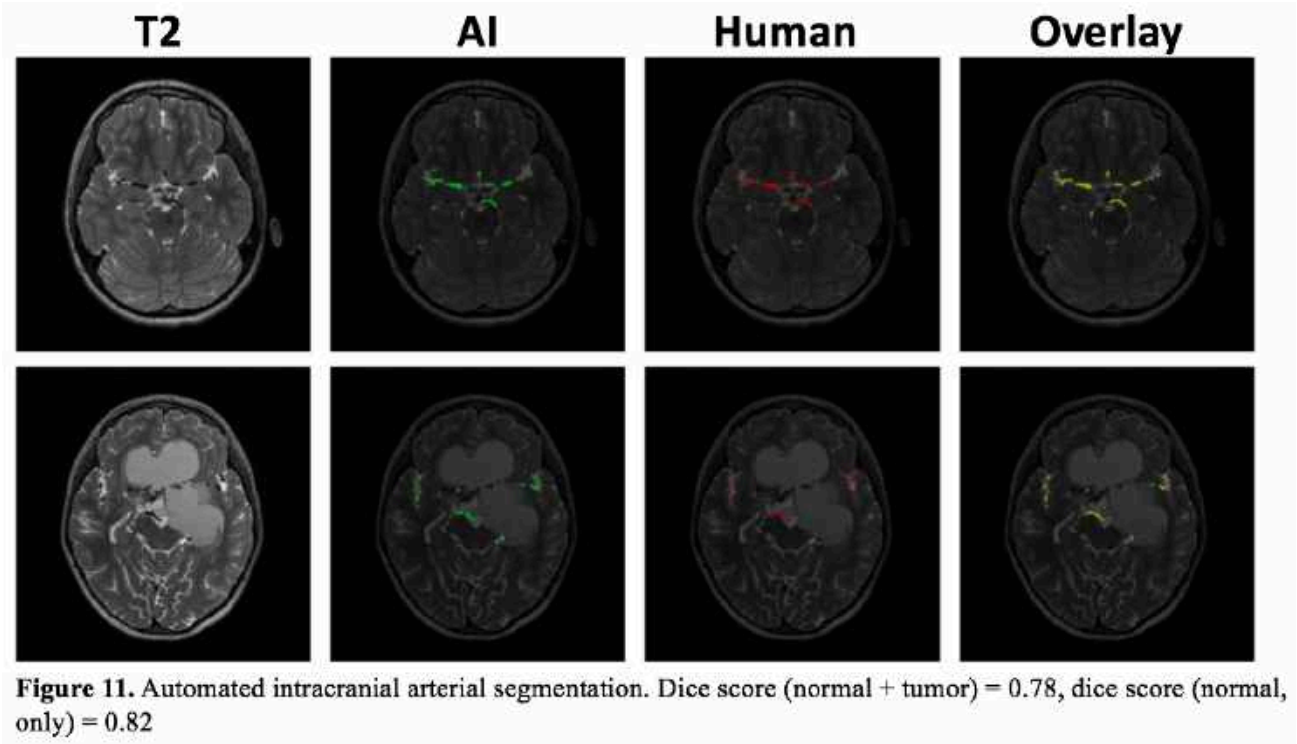

Figure 11. Automated intracranial arterial segmentation. Dice score (normal + tumor) = 0.78, dice score (normal, only) = 0.82

Conclusion

The purposes of my presentation here today is to think more critically about how we can better utilize all the data that we have collected. And these data need not necessarily be exclusively image-based; we can integrate imaging with headache profile, symptoms, or even outcomes. There are many measures that we can input. And this is exactly where machine learning comes in. We can enable machines to analyze data in a multi-dimensional space where things tend to get so complex that we could never do before. With huge computational power, perhaps we will be able to find a terrain that helps us better identify the things that we care about and create a prediction model that is clinically applicable and significant.

Thank you for your attention and I learned a lot! Any ideas that you have or even potential multi-institutional collaborations, we would love to work together.

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9.

Effects of Cranio-Cervical and Atlantoaxial Fusions on the Autonomic Nervous System

FRASER C. HENDERSON SR., M.D.

Introduction

Earlier this year we published a five-year follow up of 20 patients who had undergone craniocervical fusion stabilization for instability, basilar invagination and Chiari malformation. The study subjects were very disabled. We performed the standard intraoperative traction reduction along with fusion/stabilization.[1]

The study specifically sought to elicit symptoms that may be considered relevant to the autonomic nervous system such as syncope, dizziness, vertigo, swallowing and choking. We did see significant improvement in these symptoms, but there were also a number of autonomic symptoms that did not improve significantly. Overall, this project generated two hypotheses for us. Firstly, is dysfunction of the autonomic nervous system associated with deformity at the craniocervical junction and craniocervical instability? And if so, then is that impairment of autonomic function reparable?

In Review: Autonomic Nervous System

The spinal autonomic nervous system **(Figure 1)** exists as paired sympathetic spinal efferents from T1 to L3 which exit through the ventral root. Exiting from that root, it continues through the white ramus and forms paired paraspinal ganglia. Post-ganglionic unmyelinated fibers then re-enter the spinal nerves through the gray rami, and travel to the end organ of interest. Alternatively, the post-ganglionic fibers will pass through to the pre-vertebral unpaired superior mesenteric or the inferior mesenteric ganglia. Pre-ganglionic sympathetic fibers may also travel to the adrenal medulla which, in effect, serves as a post-ganglionic nervous system. It is also important to keep in mind that there are also sensory fibers that re-enter the ventral rami that may influence autonomic function.

In the superior sympathetic ganglia, fibers rise along the carotid, and then enjoin the ophthalmic artery and the ciliary branch, causing mydriasis of the eyes.

Cerebral circulation is largely controlled by autoregulation, but superior sympathetic fibers running through the carotid and the vertebrobasilar system can decrease vessel caliber. On the other hand, the parasympathetic fibers running through the superior salivatory nucleus and sphenopalatine ganglion can relax the vessel caliber via peptidergic transmitters and other means.

The hypothalamus is considered the "head" ganglion because within it, there is a topographical representation of many parts of the body. Stimulation of the hypothalamus can cause cardiovascular, respiratory, GI or genitourinary changes.

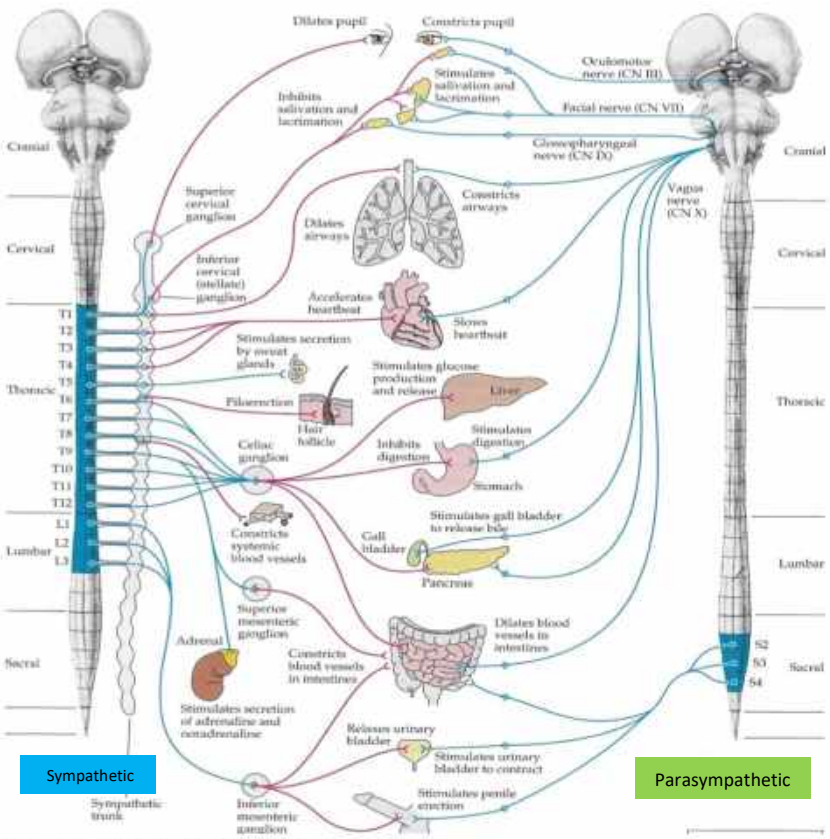

Figure 1. The autonomic nervous system

However, the hypothalamus is more of an "integration station", because it receives fibers from the cortex, from the parabrachial nucleus, from the amygdala as well as from the autonomic nervous system. The hypothalamus serves to coordinate the autonomic and endocrine functions, and also the behavior of the person, to restore homeostasis. The hypothalamus accomplishes these tasks through a number of intrinsic cells that analyze CSF glucose and serum osmolality, fibers from the medial forebrain bundle, fibers from the cortex. This intense organization takes place in the hypothalamus, at which point, it transmits fibers from the parabrachial nucleus to parasympathetic neurons in the medial part of the nucleus, and to sympathetic neurons in the posterolateral paraventricular nucleus. The control of the hypothalamus is such that deviation from certain set points within the hypothalamus will trigger change in behavior to correct the perceived abnormalities.

The Locus Coeruleus encompasses half of the noradrenergic neurons of the brain. Stimulation of the locus coeruleus is like switching on a light, with immediate electrification of the entire brain, which is critical for all cognitive functions such as attention, arousal, emotion and stress. These cells of lie right next to the fourth ventricle. This is an ascending and descending

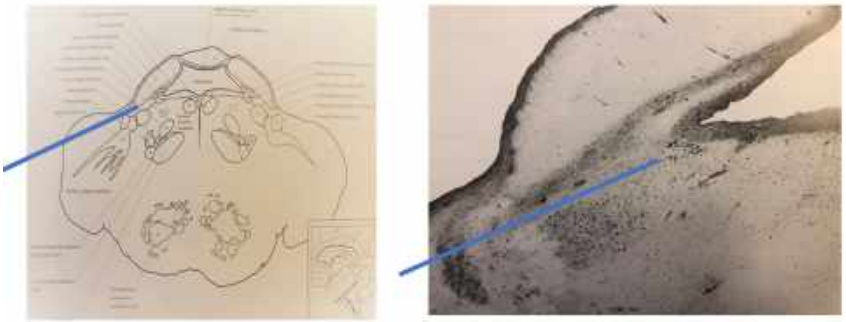

Figure 2. Locus coeruleus effect on hypothalamus and behavior.

autonomic nucleus, robustly integrated into the cortex, the hypothalamus and profoundly affecting the organism's behavior. **(Figure 2)**

A disordered Locus coeruleus can result in depression, panic, and anxiety. It is also associated with Parkinson's disease, post-traumatic stress disorder, and ADHD. The locus coeruleus affects the amygdala, which has now been shown to profoundly affect the Papez circuit: the hypothalamus, the amygdala, the mamillary body, the mammillo-thalamic tract, the anterior nucleus of the thalamus, and the cingulum. From the cingulum, the influence extends to the entire cortex.

The point of all this is that the influence of the autonomic nervous system extends far beyond the maintenance of homeostasis, meaningfully impacting cerebral activity and thought. The autonomic nervous system can provoke emotion, and can alter the understanding of subsequent stimuli. The effects of these triggered emotions can *precede the cognitive understanding* of what's happening, thereby affecting the organisms thought process of the event.

To review some anatomy in addition to the cranial parasympathetic nerves to which we have already alluded, there are also the sacral nuclei (at S2, 3 and 4) nearer the conus medullaris. In the brain stem, there is the *general visceral motor column*. The nucleus of Edinger-Westphall causes pupillary constriction. The dorsal motor nucleus, through the vagus nerve, affects all of the organs of digestion.

The nucleus solitarius is similar in some respects to the nucleus of the trigeminal nerve. It lies dorsally in the medulla, and it is topographically representative of the cranial nerves, the respiratory system, the cardiovascular system, and the GI tract. It receives input from all over the body and projects to the medial forebrain, the hypothalamus, the amygdala and other structures. If there is an increase in blood pressure, there will be increased signaling through the baroreceptors in the carotid and the aortic arch, ascending in the glossopharyngeal and vagus nerve respectively. This impulse triggers the nucleus solitarius, then causes signaling in the caudal ventrolateral thalamus which, through glutamatergic nerves inhibits the rostral ventrolateral thalamus, in turn decreasing the stimulation to the sympathetic nerves in the hypothalamus. This results in a decrease in the sympathetic stimulation of the heart, and subsequent lowering of blood pressure.

While the predominant function of the heart is controlled in a more autoregulatory manner via Starling mechanism, sympathetic stimulation can increase cardiac output to 20 liters per minute. The sympathetic ganglia (T5 and T6) exerting through the sinoatrial and atrioventricular nodes, act on the α-1 and β-1 receptors to increase the heart rate and the strength of the heartbeat. The vagus nerve on the other hand, hyperpolarizes the membranes causing a decrease in the excitability of the pacemaker cells.

Another important visceral motor component of the autonomic nervous system (ANS) is the nucleus ambiguus. **(Figure 3)** Located more ventrally in the medulla, it is involved with patterned responses such as swallowing, vomiting, breathing, coughing, sneezing and hiccups.

The ANS also influences renal function. A decrease in blood pressure sensed in the nucleus solitarius results in increased sympathetic tone via the splanchnic nerves in the mid-thorax. These innervate the β-1 receptors of the juxtaglomerular cells to trigger renin-angiotensin release, increasing sodium absorption and resulting in an increase in blood pressure. The airways are controlled mainly by the vagus nerves through the M1, M2, and M3 receptors. The C5 afferents, which pick up smoke and other noxious stimuli, trigger constriction of airways, increased permeability, leaky vessels, and increased mucus production.

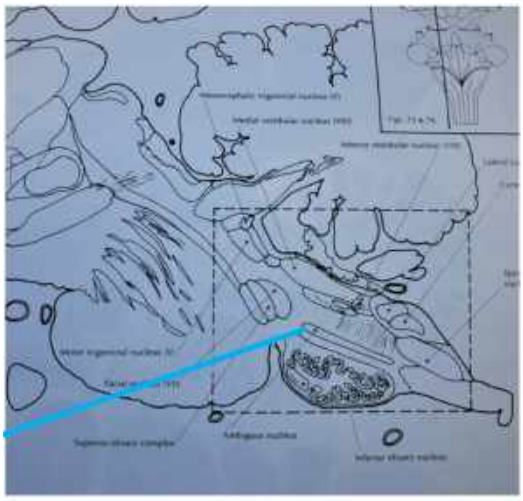

Figure 3. Nucleus ambiguus

The enteric nervous system functions as a third part of the ANS and is— to a large extent— a nervous system unto itself, partially influenced, but not controlled, by the ANS. Generally, the vagus nerve increases peristalsis in the gut, and the sympathetic nerves decrease peristalsis and blood flow to the bowel. The vagus nerve influences the bowel down to the splenic flexure. From the splenic flexure down, the sacral nuclei provide the parasympathetic influence of the bowel. There are a number of disorders that occur in the GI system as a result of dysautonomia. These include acid reflux, bloating, constipation, incontinence.

Disordered ANS function may also result in Raynaud's-like phenomena— altered blood flow in the hands, sweating, poor heat tolerance, hypothermia, and chronic regional pain syndromes.

Hypothesis and Methodology

We hypothesized that deformity, instability or perhaps turbulent or obstructed CSF flow around the medulla and upper spinal cord are associated with dysfunction of the autonomic spinal nervous system. We further hypothesized that the restoration of physiological alignment and stability of the craniocervical junction might be associated with improvement of the symptoms related to a dysfunctional ANS.

Instability at C1-C2 is well-known to occur in patients with Ehlers-Danlos syndrome.[2] It has been well recognized in other disorders, such as Down syndrome, in which approximately 25% of patients have unstable transverse ligaments.[3] Prior to the introduction of disease modifying drugs, rheumatoid arthritis yielded 50% of patient's rate of instability of the transverse ligament.[4] There are also many other disorders where we see a great deal of atlantoaxial instability because it is the most mobile joint in the body.[5-7] Of course, there is an increased prevalence of atlanto-axial instability (AAI) and cranio-cervical instability (CCI) in the Ehlers-Danlos Syndrome (EDS) population. One manuscript reported 60% of their subjects with EDS Type 4 had atlantoaxial instability.[3]

In a review article authored by myself, Dr. Benzel, Dr. Ellenbogen and others, we recognize that AAI was one of the spinal manifestations of the Ehlers-Danlos syndrome.[8] Others have recognized the presence of dysautonomia with atlantoaxial instability.[9-11]

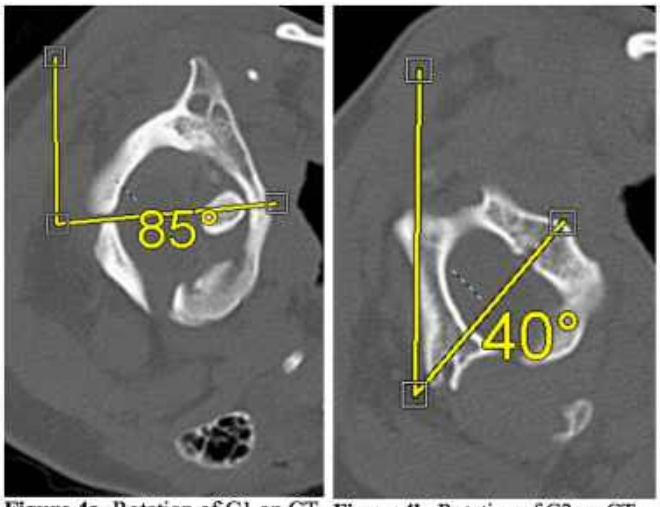

Figure 4a. Rotation of C1 on CT. **Figure 4b.** Rotation of C2 on CT.

To study all this in more detail, we evaluated a cohort of 20 subjects with hereditary connective tissue disorders from 2016 to 2018. All disorders were a result of alar ligament incompetence, not the transverse ligament. Twenty of 24 subjects responded to the questionnaire. The questionnaire was particularly long which made follow-up difficult, but it was administered by a third-party, helping to reduce reporting bias. All radiologic measurements were made by neuroradiology.

Indications for surgery included disabling headache, neck pain, severe cervical medullary syndrome, congruent neurologic deficits, and appropriate radiological findings. The patient also had to have failed all non-operative treatments.

To define the alar ligament incompetence, we placed the patients in the CT scanner, and simply turned the head to the left and then right. When the head was turned, we were able to observe C1 rotated 85° and C2 at 40°. **(Fig. 4a-b)** The angular displacement is 45°. Dr. Menezes showed that at 45° angular displacement there is no flow through either vertebral artery[3]; others describe decreased vertebral flow beginning in the high 30 degree range. The observed subluxation shown in **Figure 5** matches the Fielding, type A rotary subluxation.

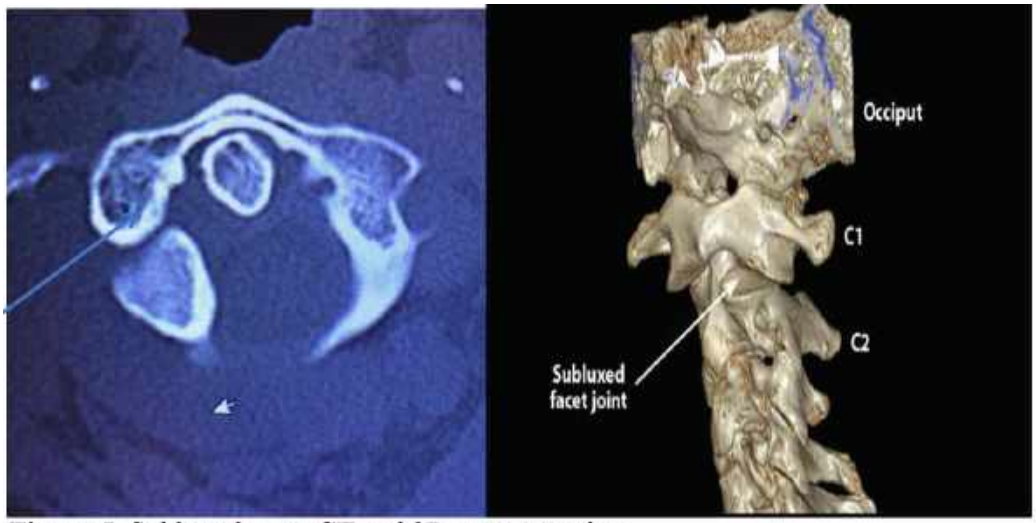

Figure 5. Subluxation on CT and 3D reconstruction.

There were a plethora of symptoms observed in this study, most of which, in aggregate, would constitute the cervical medullary syndrome. The physical findings of the patients were also very interesting. All had hypoesthesia to pin prick. The patients could feel the pin but it did not cause pain. Nineteen of 20 had C1-C2 tenderness. Eleven had decreased facial sensation. Almost all patients had hyperreflexia. Smaller proportions of these patients had weakness, decreased reflexes, difficulty with heel to toe walking, positive Romberg sign and dysdiadochokinesia upon examination. A standard fusion/stabilization with C1-C2 screws and allograft was performed on all patients included in this study. **(Figure 6)** All of the subjects had fairly profound autonomic nervous system dysfunction. We will review some of the individual symptoms of this dysfunction, in regard to results, after this surgical intervention.

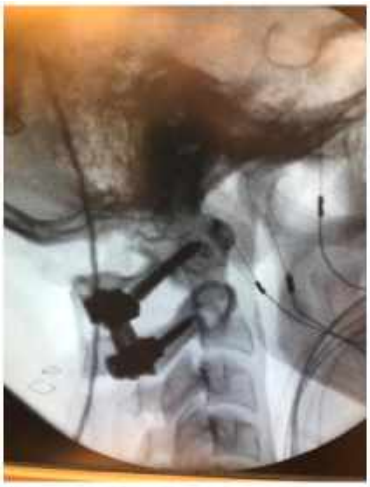

Figure 6. Visualization post-operatively

Results

Postoperatively, we saw a significant improvement in syncope, both in degree, and frequency ($p = 0.02$). In **Table 1a-b**, the red bars indicate symptom intensity and frequency prior to surgery, while blue bars indicate the same after surgical intervention.

We also assessed presyncope, meaning an event wherein the individual recognized a syncopal episode coming on, and instead would sit or lie down until the episode passed. Presyncope improved significantly at a p-value of 0.025. The frequency of presyncope, decreased significantly, as well. ($p = 0.005$).

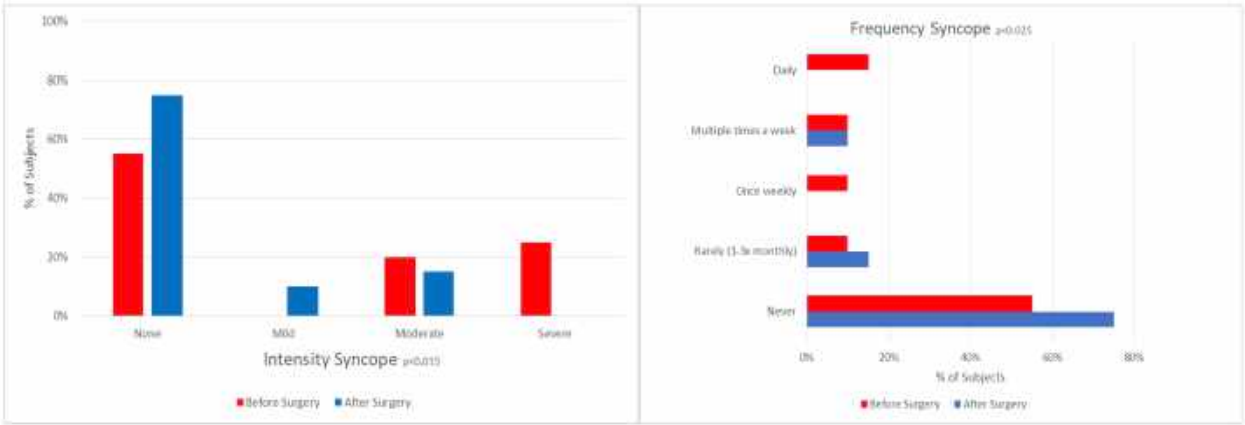

Table 1a-b. Intensity and frequency of syncope before and after fusion stabilization.

Exercise intolerance also significantly improved. In **Table 2**, again, red represents pre-operative and blue post-operative results. You can see that the amount of a severe exercise intolerance shown in the far right was decreased a great deal at a p-value of 0.007. There was a significant decrease in vertigo ($p = 0.059$). The frequency of vertigo substantially improved with the p-value at 0.008. There was also an improvement in average lightheadedness ($p = 0.057$), and the activities of daily living were moderately improved, though not necessarily at a level of

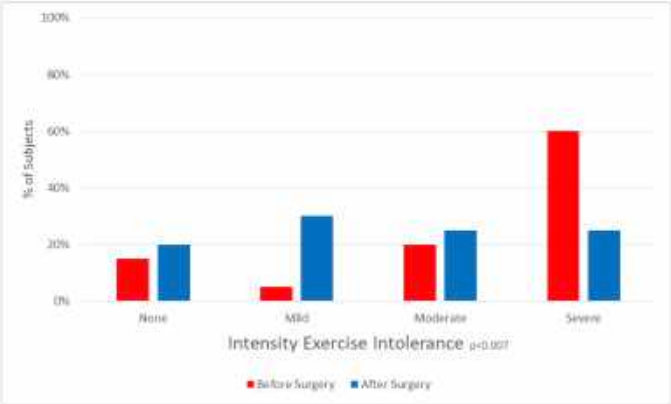

Table 2. Intensity of exercise intolerance before and after fusion stabilization.

significance (p = 0.11). Average severity (p = 0.057) and frequency (p = 0.018) of dizziness significantly decreased. Average nausea significantly improved (p = 0.045), as did its frequency (p = 0.021).

There was no significant improvement in orthostatic hypotension, which we postulate may be due to the fact that orthostatic hypotension often originates from more peripheral issues such as dilating veins and peripheral neuropathy. However, the frequency of drops in blood pressure showed a trend to decrease. (p = 0.11).

Since all subjects had some level of dysautonomia, we used a score previously developed by Dr. Peter Rowe at Johns Hopkins University and assessed the scores for each individual. Scores were assigned as negligible (0-50), mild (50-100), moderate (100-200), and severe (200-300).

Scores for each of the 30 symptoms were assessed based on severity and frequency, and a total score was developed for each subject in this study. In **Table 3**, we can see that overall average score for autonomic symptoms in this study was 162, falling in the moderate category. The post-operative score, however, decreased to 120, and that decrease was statistically significant (p << 0.001). If only the sympathetic system is considered, there was an even more significant improvement; the overall pre-operative score was 118 and post-operatively, that score decreased to a mild score of 83 (p << 0.001). There was less of an effect for the parasympathetic system. (p = 0.05). **(Table 3)**

Symptom Category	Average Total Score Pre-op	Average Total Score Post-op	Average Individual Symptoms Score Pre-op	Average Individual Symptoms Score Post-op	p-value Pre-op vs Post-op
Autonomic	162.1	120.15	4.63	3.43	**<0.0076**
Sympathetic	118.75	83.15	4.57	3.2	**<0.0063**
Parasympathetic	43.35	37	4.82	4.1	<0.053
Neurological/EDS	143.9	100.85	5.99	4.20	**<0.0056**

Table 3. Symptom scores pre- and post-operatively in this study. To summarize the degree of distress associated with each symptom, individual symptom scores were calculated by multiplying the frequency score by the intensity score (i.e., 0 = symptom not reported 1 =mild, 2 = moderate, 3 = severe for severity and 0=symptoms not report, 1=1-3x monthly, 2=1x weekly, 3=multiple times weekly, 4=daily for frequency) resulting in range 0–12 for each symptom. We calculated a Total score for each person by summing the individual symptom scores for each category. We had a total of 59 symptoms and divided into groups Autonomic (35-range total score possible 0-420), Autonomic subdivided into Sympathetic (26-range total score possible 0-312) and Parasympathetic (9 range total score possible 0-108), and Neurological/EDS (24 range total score possible 0-288) with the understanding that several symptoms may have overlapping causes. *(Method borrowed from Dr. Peter Rowe)

There were also improvements in other neurological symptoms. Headache ($p < 0.003$) and neck pain ($p << 0.001$) were both significantly improved post-operatively. Intensity of occipital neuralgia obviously improved ($p < 0.004$), as well as its frequency ($p = 0.013$). Additionally, while little is known about how to appropriately characterize "brain fog," it was subjectively reported by patients as being less intense ($p = 0.17$) and frequent ($p = 0.007$) after surgery. Hand numbness was significantly improved ($p = .0002$), as was numbness throughout the rest of the body ($p = 0.002$) and the frequency of arm weakness ($p = 0.024$).

The Wood Mental Fatigue Inventory showed no significant improvement pre- and post-surgery. The SF-36 is a well-validated scale of general well-being, and it did show significant improvement of vigorous activities: bending, kneeling, stooping, walking several hundred yards, walking more than a mile— all of these were significantly improved. ($p = 0.009$). Subjects' Karnofsky performance scores showed significant improvement at 1 year.

Patient satisfaction surveys showed that 70-75% strongly agreed/agreed that they would repeat the surgery, given the same circumstances. Others showed less enthusiasm for surgery, and two of the twenty subjects would not repeat the surgery. The patient's global impression of change showed that two thirds of subjects reported they were moderately or definitely a great deal better.

Study Limitations

One third of patients reported no change, about the same, or worse on their global impression of change. We deduce that this might be due to the fact that these patients had at least 2 other co-morbidities. These co-morbid conditions included mast cell activation syndrome, tethered cord, subaxial instability, CSF leak, transverse sinus stenosis, SI joint dysfunction, Tarlov cyst, trigeminal neuralgia, et cetera. Therefore, there were multiple comorbid confounding conditions. There were, therefore, a number of co-morbid conditions that may have limited our ability to assess these patients. This is also a retrospective study, and patients may have been subject to recall bias. This cohort was also particularly small, and a greater powered study may have demonstrated other results. There was no control for placebo effect. And lastly, all of the subjects had hereditary connective tissue disorders, so it is not known to what extent these results can be applied to the general population.

Complications

One patient had a fractured C2 screw; we later found that she also had craniocervical instability between the cranium and C1. She required an extension of her fusion up to the occiput. Other complications included one of each of the following: lumbar shunt, lumbar spinal fusion, tethered cord release, occipital neurolysis, and ICP monitor placement for intracranial hypertension.

Discussion

What causes dysautonomia? The Framingham study showed that 3 percent of men and 3.5 percent of women have dysautonomia. They attributed this due to the activation of cardio-

inhibitory vasodepressor reflex, or in some cases orthostatic hypotension, or even cardiac output problems, or an increase in resistance. What we do know is that syncope has been demonstrated with syringomyelia and Chiari malformations.[11] In the EDS population, three-quarters of the population have significant *postural orthostatic tachycardia syndrome (POTS)*.[10] A tilt table evaluation will demonstrate an increase of heart rate of 30 beats/minute. Conversely, the same population may show *neurally-mediated hypotension* , in which there is a sudden drop in the blood pressure. Both POTS and neurally-mediated hypotension are common in *chronic fatigue syndrome*. These phenomena are generally attributed to dilation of the veins and arterioles and pooling of the blood in the lower extremities with prolonged standing.

We must consider that autonomic impairment is multifactorial and that the system itself is very stratified from the brain, to the brainstem, the spinal cord, and the peripheral nerves. Some groups believe that dysautonomia in the heredity connective tissue disorder population may be resultant from the peripheral sympathetic nerves[12], but I think we've shown today that there is, indeed, a central component to this syndrome, as well.

The relationship, then, between dysautonomia and cranial cervical deformity may be inferred by the location of the autonomic nuclei and fiber tracts lying just dorsal to the corticospinal tracts. In rodents, the sympathetic nerves are demonstrated just posterolateral to the pyramids; inferiorly in the spinal cord, the autonomic fibers assume a position in the dorsal lateral spinal cord, where they are vulnerable.[12] Arguably, medullary nuclei are perhaps more vulnerable through proximity. If you are evaluating Chiari malformation, retroflexed odontoid, or instability, it is likely that they may impact these nuclei.

So, why would deformation of the central nervous system alter neurological functions in this way? We have previously demonstrated axonal retraction balls in cadaveric brainstem and spinal cord sections of subjects who had died as a result of basilar invagination from rheumatoid arthritis. These retraction balls were the result of stretch injuries.[13] A few years later, Dr. Povlishock showed that stretching nerves causes clumping of the neurofilaments and dissolution of the microtubules.[14] With injury and dissolution of the microtubules, there is a clumping of the axoplasm and formation of *axonal retraction balls*. Eventually there is an axonotmesis. Saatman histologically demonstrated the same retraction balls after stretching a mouse optic nerve 20% of its length (strain = 0.2).[15] Arundine showed up-regulation of n-methyl-d-aspartate receptors in response to stretch injury— making the neurons more sensitive and susceptible to free radical injury.[16,17] Other forms of toxic injury cause mitochondrial changes, even apoptosis. Wolf demonstrated alterations in the sodium channels pre- and post-stretch. Increase Na++ channel expression resulted in toxic calcium influx into the neurons.[18] Shi demonstrated a decrement in the compound action potential of nerves under stretch. The greater the stretch, the more decrement, and the more rapid the stretch, the higher the decrement in conduction.[19]

We looked at this notion that a kyphotic flexion deformity results in strain and out-of-plane loading, resulting in pathological deformative stress.[13] The summation of strain (stretching) and out-of-plane loading (compression)— such as occurs from a retroflexed odontoid— is referred to as *von Mises stress*. Von Mises stress and the maximal principal strain are two parameters that have been shown to correlate with tissue neural damage.[13,18,20-22] We developed a *finite element analysis* to assess von Mises stress in the brainstem and the spinal cord and demonstrated

significant improvement in the von Mises stress in the corticospinal tract, dorsal column and nucleus solitaries.[13]

Moreover, these improvements correlated very precisely with the improvement in pain and neurological symptoms. One example was a young man who was taken to the emergency room with apnea and cardiac issues on a weekly basis. He had severe bradycardia, a Chiari malformation and cranio-cervical instability. The calculated von Mises stresses were very high. After reduction fusion stabilization, he returned to normal. The subject improved, received a scholarship for Aerospace Medicine at Columbia University, received his pilot's license and is doing very well 15 years later. The improvement in stresses was correlated with ASIA and Karnofsky scores as well as the physical and mental component of quality-of-life. And despite the small number of cases in that study, the *p* values were quite high.[13]

So, autonomic nervous system dysfunction— dysautonomia— is associated with cranio-cervical and atlanto-axial instability. This association was statistically significant in the population of subjects studied. There was a statistically significant improvement of autonomic symptoms that occurred following reduction of deformity and stabilization.

It is important to recognize that the autonomic nervous system is vertically integrated with the hypothalamus, the brainstem nuclei, the diencephalic structures and cortex. The autonomic system is fully integrated in response to environment, emotion and homeostasis. It also assumes a significant role in preparing us for action and for communicating emotion to others. These responses not only precede, but influence cognitive appreciation of goings-on. Our behavior is influenced by brainstem nuclei.

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10.

Dural Histopathological Changes in 139 Cavalier King Charles Spaniels with Chiari-like Malformation

CATHERINE A. LOUGHIN, D.V.M.

Introduction

Thank you for staying for the veterinary portion of the program. Most of you know who I am, Dr. Catherine Loughin. I am originally from Cleveland, but I have been transplanted to Long Island for about 18 years now. It is there that I have been working closely with Dr. Dominic Marino, whom most of you know. He is on the Scientific Educational & Advisory Board of Bobby Jones CSF. We have been working on this Chiari project for probably 15-16 years, for about as long as we have known Dorothy Poppe. Today I will present just one of the studies that has come out of that ongoing project.

I have been sitting in on a lot of the meetings this weekend, and there has been a lot of talk about databases. That is something that we have done with this project. We have been collecting information on not just Cavaliers, but on all small breed dogs affected with Chiari throughout the course of the project.

For those who have not heard any of our previous lectures, the study involves a full body MRI of these animals. So, imaging is done from nose-to-tail. The dogs that have syringomyelia, also get pre- and post-operative cineMRI. There are also CT scans of the head and neck, a thermography, and a hearing test.

So far, we have collected a lot of data from about 400 dogs included in this dataset. Hopefully, as the years go on, we will be giving you more and more information.

I am not the primary author on this paper. The primary author was actually one of my residents, Dr. Jaclyn Holdsworth, who is now a staff doctor and has been working on this project for about 4 to 5 years. We hope to have this paper published very soon. Also named on the paper are Dr. Martin Lesser, our statistician who has worked on all our papers, Joseph Sackman, one of our research assistants who has been working with us for a long time, and Marissa O'Donnell, a more recent addition to our team.

I will not go into a lot of detail because most of you have heard our previous presentations on Chiari malformation (CM) in dogs. CM has been described in small breed dogs and happens to be especially common among Cavalier King Charles Spaniels, but it is not just a Cavalier problem. One day, I will come to this meeting with my database on all small breed dogs and be able to tell you the difference but right now, for the most part if you look at veterinary studies, they are almost all done on Cavaliers. They just happen to be the breed that has the most problems.

I'll briefly go over the presenting clinical signs of CM that you may not see in your human patients as a means of review. There is a lot of scratching, especially in the Cavaliers. Sometimes they make contact with their head and neck, but there is also a lot of "air scratching". When a dog air scratches, they are feeling a tingling sensation and that results in them scratching at nothing. A lot of them have head, neck, thoracic and lumbar pain upon exam and they also have

cerebellovestibular dysfunction. Overall, we see a lot of different signs, but these are particularly common among Cavaliers.

We have been talking a lot about what it means to come to consensus on CM diagnosis and treatment this weekend. There certainly is a lack of consensus in the veterinary world, as well. In doing the background work for our study, we did a lot of reading in the human medical literature, many papers written by individuals in this room. It was almost comforting to learn that there is no consensus in humans regarding duraplasty and other controversies, as well. There is a lot of work that needs to be done on both ends, veterinary and human. And we certainly hope that some of our work will help you with yours. Personally, I am very interested in the results of Dr. Limbrick's comparative effectiveness study on duraplasty.

In veterinary medicine, the big controversy that we have still not surmounted is the actual decision to do surgery. There are neurologists that sit on one side, claiming that surgery is not the best method for treatment and it serves more as a torture for people's dogs. And then we tend to stand on the other side, saying that this is not necessarily true because there are certainly some dogs that need the surgery in order to get better. If you look critically at the studies analyzing medical therapy only, you see that about 75% of the dogs get worse over time. At least 75% of them would likely benefit from having the surgery. So, we need to come to our own consensus on treatment options in veterinary medicine, as well.

Background

With regard to dural changes, not much was previously written in the literature for either human or veterinary medicine. However, we do see osseous compression and when we do our surgeries, we see also a thickened dural band up against the dura mater. This is when we came up with our hypothesis for this study. We hypothesized that we could use this dural band to relate back to the dog's age or the length of time during which they had clinical signs, and then compare to see how they fare after surgery.

As I was reading many of your papers, there seemed to be a significant reduction in syrinx and neurological clinical signs after a duraplasty. This is certainly something that we want to see in our own patients. Our practice is to do foramen magnum decompression (FMD) with cranioplasty. We also do a full-thickness durectomy and send that out for histopathology. We have been doing this for pretty much the entire time that we have been working on this project. Additionally, we monitor the quality-of-life. Again, the human physicians at this meeting have been talking a lot about quality-of-life questionnaires. All of our quality-of-life questionnaires are administered to the owners. Because this is analogous to questionnaire administration in pediatrics, the pediatric neurosurgeons in attendance will understand the difficulties in teasing out true quality-of-life conditions. You are largely relying on the parents to tell you about that child's quality of life. Granted, the owners are usually very on top of what is going on with their dog. It's particularly important to tease out quality-of-life in veterinary medicine, however, because there is the option of euthanasia. If you cannot improve the dog's quality-of-life, the dog can potentially lose its life. So, this is very important to us.

I actually had to ask Dorothy to help me get some of the papers written on dural histopathology because they were hard to find and some are very old. So, if Dorothy asked you for a paper on my behalf, I thank you as well. The main paper that we were using as a guide was by Dr. Nakamura and colleagues in 2000.[1] They observed that Chiari I patients with syringomyelia had hyalinosis and calcification and/or ossification. They also saw a thickened dura due to the chronicity of CM. Their presumption was fairly similar to what we were thinking: that these dural changes were presumed sequela of dissociation in CSF pressure between the cranial cavity and spinal cord. The concept being that increased pressure at the cranio-cervical junction may cause pathology in the dura.

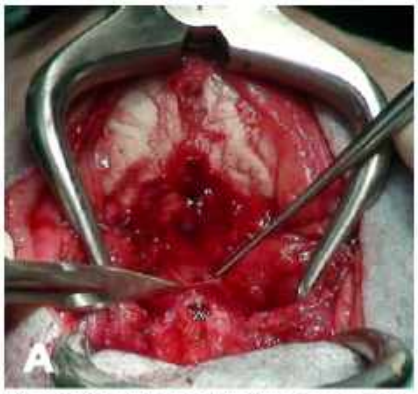

Figure 1. Standard foramen magnum decompression

Rationale

That essentially became the purpose of our study: to describe the histopathologic changes the dura in dogs with CM. We want to determine what we are seeing in the dura and relate it back to the characteristics of the dog. We started with the simple things, reporting any associations between age, presence of syringomyelia, duration of clinical signs prior to surgical intervention (granted, this is not necessarily when the dog may have felt the signs but when the dog owner reported that the dog was showing signs), and then quality-of-life pre-operatively score from 1 (poor) to 5 (excellent). We included a post-operative questionnaire and have continued surveys to follow-up for a couple of years, as part of our larger CM project.

We were able to get 139 consecutive client-owned Cavaliers included in the study, which in veterinary medicine is a lot of dogs. We would certainly love to have more dogs, but that is where we are at right now. As I said, they had a full body MRI before the surgery and then we did a FMD with cranioplasty during the surgery. They all had the dura resected and submitted for biopsy. Resections were all submitted to a single pathologist for interpretation to mitigate bias.

For those who have not seen our previous lectures, we do a standard FMD (**Fig. 1**) where we take out the suboccipital bone. We actually take the entire C1 lamina off, all the way back to C2. Then we take a snippet of C2 because in dogs, it hangs over a little bit. I will show during the slide with the plate on the dog why we do that. We actually lift up the cerebellum and look for any adhesions and veils to clear those out as well. We originally started with a different pathologist at Cornell, but she moved on, so all our specimens were re-read by Dr. Miller at Cornell. He has a pathology laboratory at a Cornell, so we wanted to make sure that there was no bias and that all the information was read consistently.

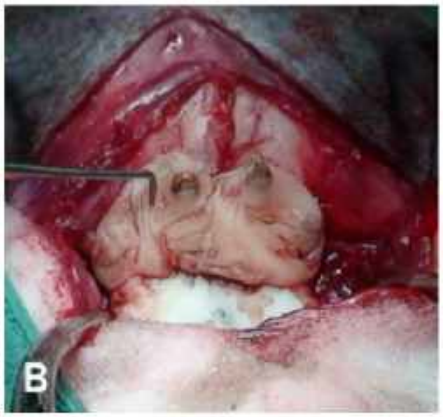

Figure 2. Cranioplasty

Figure 2 shows our cranioplasty. We put 5 titanium screws around the opening on the occipital bone and beneath that polymethylmethacrylate titanium mesh. We use titanium because we do another MRI on all of these dogs after surgery. So, they get these MRIs, for free, at six months, one year and five years after surgery. They can get more MRIs when and if there is a problem. We want to make sure that we can put the dogs through the machine without causing a problem.

About halfway through the study, we started putting a fat graft at the very back of the cranioplasty. The reason for that, the same reason that we take off a snippet of C2, is because we were finding that some of the dogs were having scar tissue grow behind the plate and up underneath the plate. So, we then had a subset of dogs, around 20%, that had to have surgery again for the scar tissue. We have had only one dog have to go in for another surgery ever since we began putting in the fat graft, significantly reducing re-operation rates on these dogs.

Histopathology of the Dura

I am not a pathologist, so I am not going to go into a lot of detail about the dura, but just for the purpose this lecture, I wanted to briefly scour the literature and describe a normal dura. It is very well described in the literature.

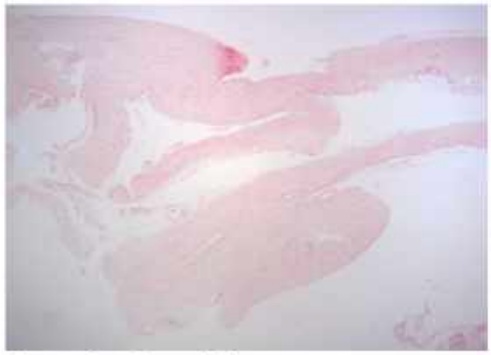

Figure 3a. Normal dura

Figure 3a shows a very clear picture of what the dura is supposed to look like—parallel layers of collagen, arranged in a ribbon-like structure. The first phase of pathology that we saw in our sample was arachnoid hyperplasia (**Fig. 3b**). The lining of the inner surface of the dura consists of foci of hyperplastic arachnoid cells. Hyperplastic cells start to fill in where all the ribbons in the normal histology are usually found. The next phase of dural pathology we saw was fibrosis (**Fig. 3c**). The normal thickness of the dura becomes distorted by a moderate expansion of fibrous connective tissue. Next, we start to see mineralization (**Fig. 3d**) which is the formation of mineralized bone found within the dura. And finally,

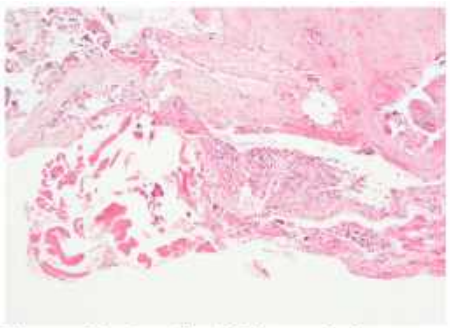

Figure 3b. Arachnoid hyperplasia

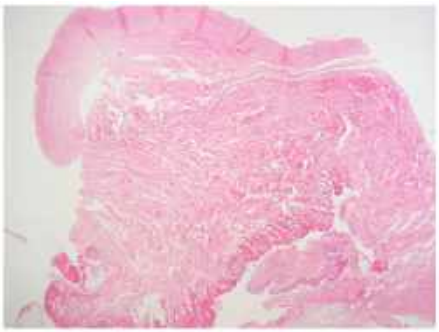

Figure 3c. Fibrosis

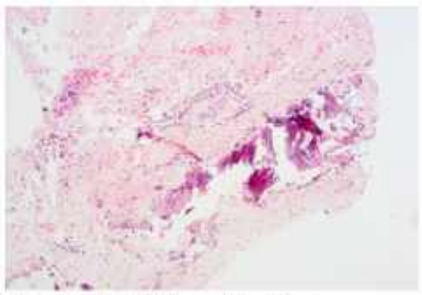

Figure 3d. Mineralization

Figure 3e. Osseous metaplasia

we see osseous metaplasia shown in **Figure 3e**.

During the peer review process, one of the comments we received was that we should really have a control group. This is an ethical problem, however. No normal human beings are going to let their healthy dogs have an unnecessary operation just to have their dura biopsied. The university also cannot just take the samples without the owner's permission. Because of all that, we added the following disclaimer: Histopathology of the canine dura is well understood and described in veterinary literature. Since the aim of this study was to describe abnormal histopathologic findings of the canine dura in a cohort of CKCS with CM, control samples were not deemed necessary.

In the end, we did not have any controls. But since there is enough information available in the existing literature about what constitutes a normal dura, we used that information as a comparative.

Methods

As I mentioned before, we used different variables to see if there were any connections. The variables are age, sex (male and female intact, male neutered, female spayed), duration of pre-surgical clinical signs, pre-operative quality-of-life score, serum chemistry and complete blood counts, syringomyelia, and dura histopathology. As I said, the pre-operative quality-of-life scale was provided by the owners on a scale from 1 (poor) to 5 (excellent). This is all based on the owner's impression of how their dog is doing. We used this questionnaire originally for our foramen magnum study back in 2007 and we are using it currently in our cranioplasty study which is hopefully going to be published soon. It's been working fairly well, so we are probably going to stick with this particular questionnaire for most of our CM studies.

The Chi-square test was used to analyze associations between diagnosis and categorical variables. For continuous measures, Kruskal-Wallis non-parametric test was used to compare distributions across the different pathology categories. We had a small number of dogs in the arachnoid hyperplasia and mineralization groups, so our statistician combined the former into the fibrosis category and the latter into the osseous metaplasia category. For the testing, we did a paired t-test using a 95% confidence interval ($p < 0.05$) to compare the pre-op and post-op quality of life.

Results

The results were that the mean age was 43 months. Dogs having this surgery are between the ages of 2 and 13 years of age, but most of the dogs that have surgery are on the younger side. The duration of pre-surgical clinical signs was about 42.61 weeks. Additionally, their preoperative quality-of-life was about 2.7 on the scale from 1 to 5— a fair/poor quality-of-life score. A total of 121 out of the 139 dogs in the study had syringomyelia, so we do see quite a lot of syringomyelia in dogs— about eighty-seven percent. Eighty of the 139 dogs (58%) had some form of dural pathology. Of those 80 pathological specimens, 4 dogs had arachnoid hyperplasia (5.0%), 23 had fibrosis (28.8%), 3 had mineralization (3.75%), and 50 had osseous metaplasia (62.5%).

We saw changes in clinical signs as early as four weeks after surgery. Again, this is dependent on owner perception of those signs, but that is pretty early for a dog. Age at the time of

decompression, the presence of syringomyelia and the pre-operative quality-of-life score were all found to be independent of the aforementioned histopathologic changes; no associations were identified.

But, more than half of our specimens did have dural pathology present. Dural pathology was seen as early as 4 weeks after the onset of clinical signs. Again, there was no association between histopathologic changes and the age, whether they had syringomyelia and the pre-operative quality-of-life score.

Conclusions

It is unknown at this time whether there is an influence of various histopathological changes on long-term prognosis in canine patients who do not have a duraplasty or durectomy because all the dogs in this study had a durectomy at the time of the FMD/cranioplasty. The data are accumulating, however. Many of these dogs are followed long term after this study—several are 10 to 12 years out. The causes of death for these dogs tend to be unrelated to CM or syringomyelia. Heart disease, probably, is the number one cause of death in the Cavaliers. The good news, though, is that most of these dogs have not passed away due to CM.

We can't really comment about whether it is preferable to do a duraplasty in veterinary medicine, and our clinic is pretty much the only one currently doing a cranioplasty. Some people just do FMD (bone, only). Others do choose to do the duraplasty. Another group does fat grafts. But overall, most other centers don't have a particularly large sample, or the sample is mixed between Cavaliers and non-Cavaliers. So, it is pretty difficult to compare studies.

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11.

Tethered Cord in Dogs

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Introduction

Thank you all for staying around to hear another dog lecture. Similar to Dr. Loughin's clinic, our lab also studies Cavalier King Charles Spaniels and their Chiari malformation and syringomyelia. Our big interest is how we can be translationally impactful with the human community. It is a real honor to be here today. I do not have anything to disclose.

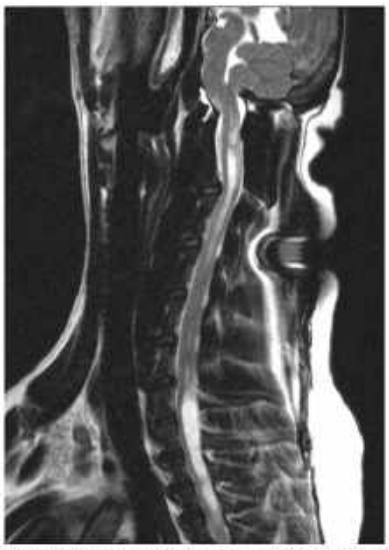

Figure 1a. MRI of canine, incorrect orientation.

It is well known in the veterinary community— and hopefully to all of you now— that Cavaliers do often have quite a few cranio-cervical junction anomalies. These have been very deeply studied and have been a focus for any researchers working with this breed regarding neurological issues.

Just as a quick sidebar, I am going to show you the MRIs that we look at, just to acquaint you with them a bit. I know that you all are used to looking at sagittal MRIs in the orientation shown in **Figure 1a**, but this is really hard for those of us who treat canines to look at. For us, these mid-sagittal MRIs are flipped such that they are in the orientation in **Figure 1b**. This accounts for their quadruped stance. I just wanted to mention that at the outset and apologize in advance because this is probably going to be very awkward for you to look at throughout the presentation. Also, when I discuss directional terms, I think they may also be a little different, too, in terms of positioning in dogs. **Figure 1b** includes directional orientation, as well. We can see that when I say something is "cranial", I mean towards the head and "caudal" is towards the tail; "dorsal" is toward the back of the body and "ventral" is toward the belly. This is just to avoid confusion because we will be using those terms.

As you can probably see, the Cavalier imaged in **Figure 1b** has Chiari-like malformation. We call it Chiari-like just because it is similar to the Chiari condition in humans, but it is more of a loose definition for veterinary practitioners. There is herniation and indentation of the cerebellum and a clear volume loss. You can also see that the syringomyelia is present in the cervical spinal cord. It also tends to interrupt the caudal cervical spinal cord and kicks back up into the

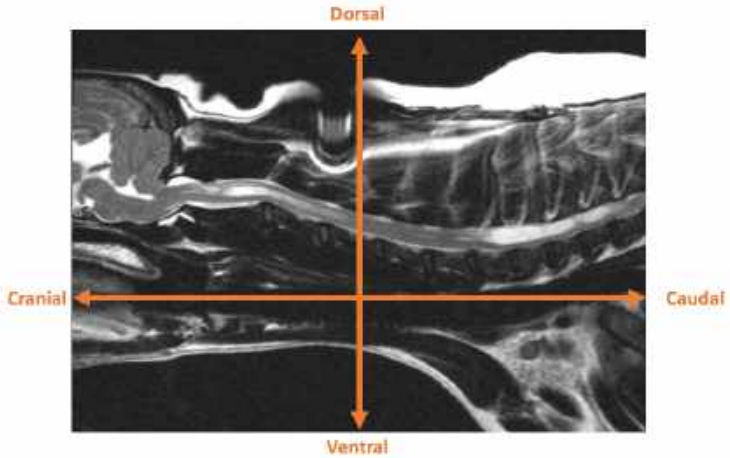

Figure 1b. MRI of canine, correct orientation.

cranio-thoracic spinal cord. Taken together, these conditions, as was mentioned previously, cause neuropathic pain and a lot of times itching around the head and neck region for these dogs.

Background

Interestingly, over time, we have noticed that these dogs display clinical signs situated more caudally. Profound lumbar spinal pain upon palpation is pretty common. Often, as well, we may see gait abnormalities. Whether it is just hind limb weakness, or what we call "the Cavalier shuffle"— they just look odd and tend to swing their hind legs they are abducting excessively when they are protracting their hind limbs.

To learn more about these caudal anomalies, we started getting images all the way down to their tail. Like Dr. Loughin mentioned earlier, most neurologists are still only imaging the head and neck region of these dogs. Surgeons, however, are starting to look all the way to the tail. Commonly, what we wind up seeing is that these Cavaliers have a syrinx present in the thoracic and lumbar spinal cord as well, or they may have a holocord syrinx. This is important to note, since we were clearly missing a lot of this before when we were only imaging the cervical spine. All of these findings have led us to wonder if there is something else going on more caudally? Is there a caudal-spinal anomaly that we should be paying attention to? It is clearly a supposition at this time, but since we are now seeing these things occur so frequently, we think that they should be addressed.

Being the Ph.D. student that I am, I felt obligated to try to read all of the literature about caudal anomalies in human Chiari. I came across these reports of human Chiari patients with syringomyelia and tethered cord syndrome.[1-6] I know that these papers are controversial, and I have read both sides of the story here, but I just thought it was really interesting that some patients seem to have co-existing conditions and that it warranted some academic study in canines, as well. Recent work was also done, modeling the spinal cord in canines to determine how syringomyelia develops in the cord and one of the conclusions that the authors made was related to spinal cord tethering and its potential implication in thoracic-lumbar syringomyelia development.[7] All of this evidence got our minds rolling and we decided to take a look.

Methods

We started by simply looking at MRIs and doing a retrospective MRI study to see if we could find anything of interest in the caudal spinal cord.[8] Our specific aims were twofold. First, we wanted to look at Cavaliers and weight-matched breeds to see if there is any difference in spinal cord or dural sac termination using MRI. We looked at dural sac termination too just because it is very easy to pick up on HASTE sequences. Then, our second aim was to investigate whether the presence of syringomyelia (more so, thoraco-lumbar syringomyelia) in Cavaliers, would be associated with these termination sites. We hypothesized that Cavaliers would have a more caudally terminating spinal cord and dural sac compared to weight-matched breeds and that thoracolumbar syringomyelia would be associated with these termination sites. Again, we really did not think that we would actually find any differences, it was just something that we thought we might look into for the academic pursuit.

For specific aim one, we scanned our local MRI database between the years of 2004-2017 for Cavaliers and weight-matched breeds that had thoracolumbar MRIs. We looked for brachycephalic and non-brachycephalic controls. I know that word may be foreign to most, but what brachycephalic means is short headed and short-snouted dogs. If you think of a brachycephalic dog, you might picture a pug, Shih-tzu, or a Pekingese. We were sure to do this because we wanted to account for tight skull morphology. We also used non-brachycephalic controls like beagles, Jack Russell Terriers or poodles. All dogs were imaged with 1.5 Tesla MRI. Next, we filtered out all cases based on of report keywords because we wanted to make sure to exclude any cases that had diagnoses that could impact the position of the spinal cord. From there, the images were anonymized and reviewed. I was blinded because I was the reviewer. The breed ID was also pulled out, so I did not know which case was what breed. Again, these images were evaluated for image quality to make sure that we had everything that we needed.

For specific aim two— again, comparing Cavaliers with and without syringomyelia— we filtered images in the same fashion looking for Cavaliers with both cervical and thoracolumbar MRIs. We also filtered, using keywords just like in specific aim one. We then separated cervical images from the associated thoracolumbar images of the same patient and gave the images different study names to ensure that the reviewer (again, me) did not know the images had come from the same patient.

To make our observations, I worked with the radiologist at the veterinary school to define the termination sites ahead of time. I needed these sites to be simple, so what we ended up coming up with is shown in **Figure 2**. Looking at these T2 sagittal images on the left, I looked at lumbosacral region and would determine if the spinal cord was no longer tapering. I then would use the corresponding transverse or axial views (right) to see if there was any spinal cord signal or T2 hypointensity in that slice. I wanted to get to a slice where that signal was lost. In row B, I felt comfortable saying that the spinal cord signal was lost and that level is probably entering into the filum terminale. I used the corresponding T2 sagittal view to identify the spinal segment and vertebral location of that lost signal on axial view. In this case, this dog was terminating at L7. With regard to the dural sac (row C), this patient illustrates a good representation of why we chose to look at this outcome measure. Looking at side-by-side T2 and HASTE views, I was able to find the end of the dural sac and find the corresponding vertebral location using the T2 image.

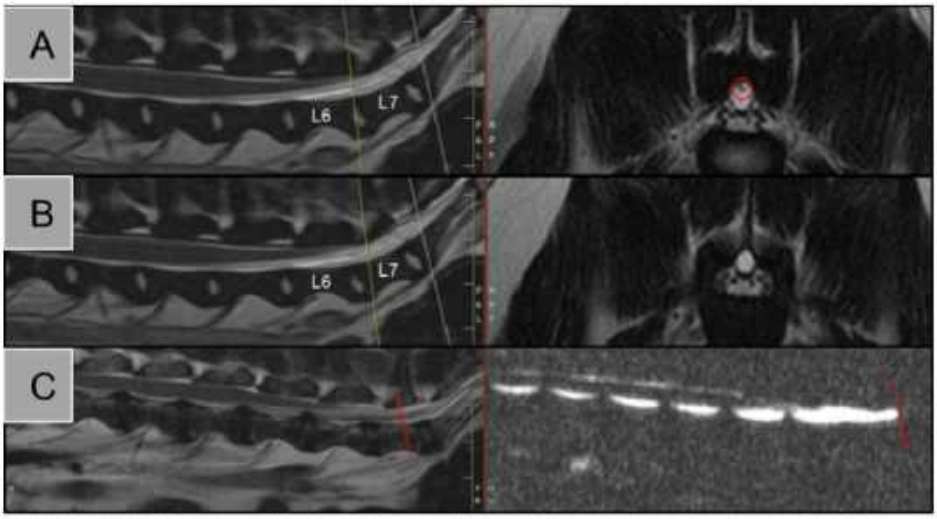

Figure 2. Pre-defined termination sites. (Sparks et al., 2019)

Comparison	Statistical Test
Intra-observer reliability	Kappa analysis
Breed vs. termination sites	Chi-square tests & contingency tables
Maximum SM height vs. termination sites	Wilcoxon rank sum test
Presence of SM vs. termination sites	Chi-square tests & contingency tables
Address Multiple Comparisons	Holm-Bonferroni Method

Table 1. Statistical analyses performed.

I am a statistics nerd, so I like to talk about statistics but I will keep it brief. Case identifiers were removed, and we only assigned the study numbers. Breed identity was also masked throughout. It is important to note that about 15% of the cases were re-scored or re-evaluated about 3 months after the original cases were done in order for us to look at intra-observer reliability. We used Kappa analyses to assess my consistency in measurement. **Table 1** illustrates the other statistical methods used. Also, I want to point out that I performed multiple comparisons in assessing my *p*-values. As you know, if you run a bunch of comparisons, you might come across something that is statistically significant, and I wanted to have further confidence in my *p*-values. I don't think this is discussed often enough for clinical trial designs.

Results

We ended up with a sample of 106 anonymized cases. Thirty-four cases were excluded based on inappropriate imaging or something was wrong with the image where we could not see what we wanted to see. We ended up with 39 Cavaliers and 33 controls. Of those 33 controls, 20 were brachycephalic and 13 were non-brachycephalic. **Table 2** shows that the Cavaliers and control dogs were not significantly different with respect to age, sex, and weight.

Figure 3 shows some representative sagittal MRIs for the three breed groups— Cavalier, brachycephalic control and non-brachycephalic control. Obviously, we picked pretty images that we thought were the best representations. You can see in these images that the spinal cord is terminating in the sacrum for the Cavalier. For the two control breed groups, the spinal cords were terminating more cranially around L7, which is relatively normal according to the veterinary anatomy books. I should note that our Kappa value for intra-observer reliability was 0.6 which is about moderate for this measure.

For our dural sac termination, The Kappa value for dural sac termination was better: 0.8. This means that it was easier for me to repeat the dural sac measures reliably. **Figure 4** illustrates representative cases of

	CKCS (n = 39)	Control (n = 33)	*p*
Age (median, range)	6, 1.5 - 11	7, 2 - 15	.63
Sex (F, M)	17, 22	19, 14	1.0
Weight (median, range)	9, 5.45 - 14	7.6, 4.82 - 13.6	.09

Table 2. Cohort characteristics of Cavalier King Charles Spaniels and control dogs. (Sparks et al., 2019)

dural sac termination. We see that the dural sac terminates beyond the sacrum in the Cavalier, whereas for the control breed dogs, the dural sac terminates cranial to the sacrum.

I apologize that the next couple of figures may be a bit confusing to read at first but I will explain them. My first analysis was to compare Cavaliers to the control breeds, as a whole and **Figure 5** basically illustrates spinal cord and dural sac termination.

Starting with spinal cord termination the figure shows the proportion of dogs that terminate in each group at every vertebral location. The Cavaliers are indicated in dark gray and the controls are in the lighter gray. About 10% of the dogs that terminated at L6 were Cavaliers, whereas if we move caudally towards the sacrum, about 95% of the dogs that are terminating in the sacrum are Cavaliers. So, we see there is a clear trend towards Cavaliers terminating in a more caudal location. (p = 0.0001) This holds true for the dural sac termination as well. (p = 0.002)

Taking this one step further, I just wanted to make sure that skull morphology did not play a role here. Again, since Cavaliers have a really characteristic skull, I wanted to compare with other brachycephalic control breeds that have a similar morphology to ensure this isn't the potential mechanism of this low termination. And again, we saw similar trends. **(Figure 6)**

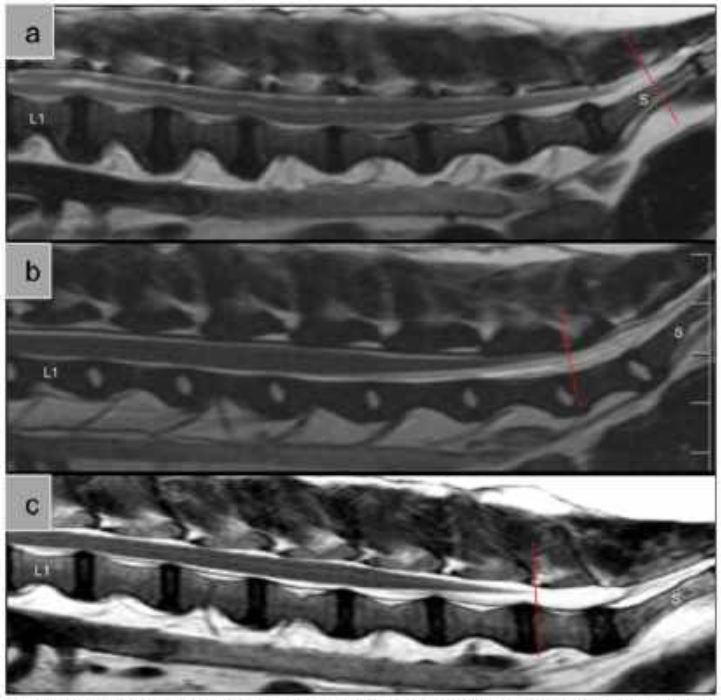

Figure 3. Sagittal MRIs representative of three breed groups: Cavalier King Charles Spaniels (Row a), brachycephalic controls (Row b) and non-brachycephalic controls (Row c). (Sparks et al., 2019)

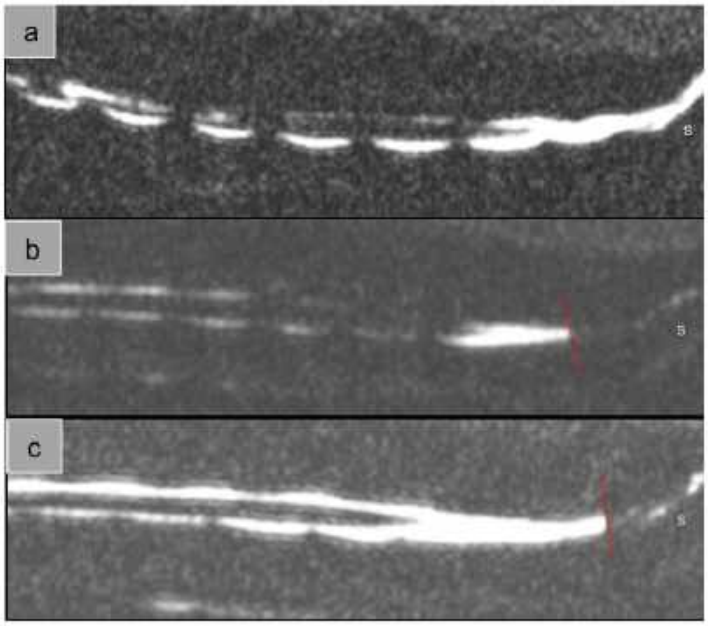

Figure 4. Sagittal HASTE images representative of three breed groups: Cavalier King Charles Spaniels (Row a), brachycephalic controls (Row b) and non-brachycephalic controls (Row c). (Sparks et al., 2019)

The Cavaliers tended to have a more caudal termination of the spinal cord. Cavaliers were also significantly different from both the brachycephalic and non-brachycephalic groups with

respect to spinal cord termination ($p = 0.002$ and $p = 0.002$, respectively) and dural sac termination ($p = 0.02$ and $p = 0.03$, respectively. The control breeds themselves, however, were not statistically different from one another in either spinal cord termination ($p = 0.82$) or dural sac termination ($p = 0.73$). Therefore, this actually seemed to confirm our original hypothesis. We were excited and, in fact, surprised by these results.

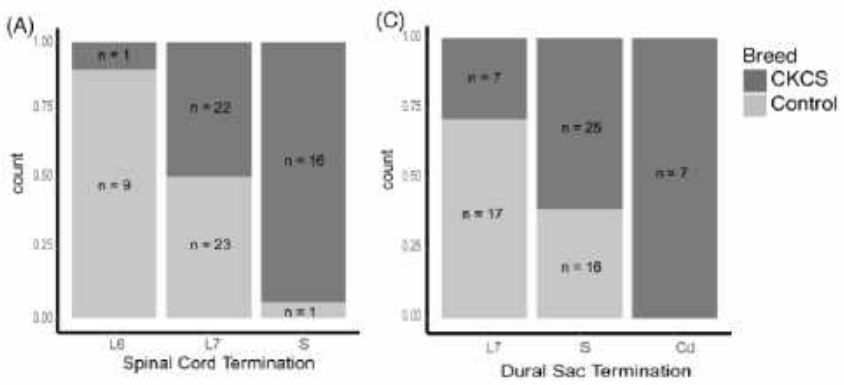

Figure 5. Cavalier King Charles Spaniels compared to all control dogs. (Sparks et al., 2019)

The results of specific aim two— to compare Cavaliers with and without syringomyelia— were a little less clear. We had 34 Cavaliers who had both cervical and thoracolumbar imaging. We ended up with 18 Cavaliers that did not have syringomyelia and 16 Cavaliers that did. Of those 16 Cavaliers that did have syringomyelia, three had cervical syringomyelia only, two had thoracolumbar syringomyelia only, and eleven had both cervical and thoracolumbar syringomyelia. It was interesting to see that there were 2 dogs that had thoracolumbar syringomyelia only. It is very rare to see that at all, and I wonder if Dr. Loughin finds that interesting as well. Concerning the hypothesis for this aim, we were really mainly interested in the dogs that had thoracolumbar syringomyelia, situated more closely to the end of the spinal cord. We would think that this has more of an association with some sort of spinal cord tethering.

When comparing the dogs with and without syringomyelia, the spinal cord termination was not significantly different, although we did see a trend in that direction. However, when we looked at dural sac termination **(Figure 7)**, dogs with thoracolumbar syringomyelia trended towards spinal cord termination in a more caudal location. ($p = 0.03$)

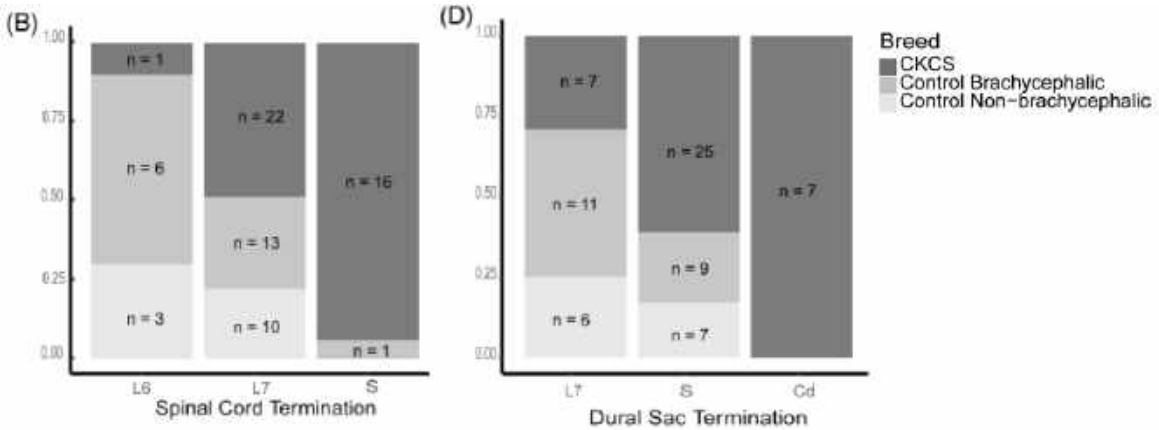

Figure 6. Cavalier King Charles Spaniels were significantly different from controls, but control dogs were not significantly different for spinal cord and dural sac termination. (Sparks et al., 2019)

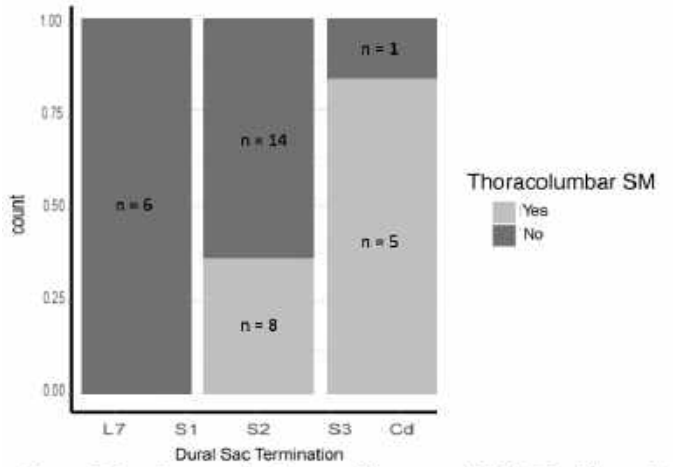

Figure 7. Dural sac termination trended more caudally in Cavaliers with thoracolumbar syringomyelia as compared to Cavaliers with no thoracolumbar syringomyelia. ($p = 0.03$) (Sparks et al., 2019)

I also thought this was interesting: **Table 3**, points out the distribution of each dog in each category. The two anomaly cases—again, we do not normally see dogs with only thoracolumbar syringomyelia—terminated in the caudal-vertebral level, which is really far back. This is in comparison to the dogs with cervical syringomyelia who had dural sac terminations located much more cranially. It is just interesting, but we know that our sample size is low and we recognize that.

Conclusions

With that, we can conclude that the spinal cord and dural sac termination occurs more caudally in Cavaliers. We have also established that there is a relationship between dural sac termination and thoracolumbar syringomyelia. This leads us to beg the question as to whether or not Cavaliers also have tethering of the spinal cord. We cannot conclude that at this point, but it is just interesting. And, certainly, if it is true that Cavaliers have tethered spinal cords we also wonder whether that spinal cord tethering may be involved in the development of thoracolumbar syringomyelia.

Study Limitations

	Cervical and thoracolumbar SM (n = 11)	Cervical SM only (n = 3)	TL SM only (n = 2)	No SM (n = 18)
Termination sites		Dural sac termination		
L7	0	2	0	4
S	8	1	0	13
Cd	3	0	2	1

Table 3. The location of dural sac termination in CKCS. The presence of SM at each vertebral location is displayed as the number, *n*, of dogs in each category. (Sparks et al., 2019)

There are several limitations to this study that must be addressed. Of course, this is a retrospective study wherein we chose cases to fit our criteria. We also had a hard time finding good control MRIs because most of the dogs imaged had some sort of pathology that could potentially complicate the cause of low spinal cord termination. We were really diligent about removing those potentially confounding cases, but we ended up with fewer controls than we would have liked. Also, we are unable to differentiate that the cut points we have chosen as spinal cord termination are actually the conus medullaris or the filum terminale. But, again, we did try to modulate that issue by reducing bias in the procedures of blinding and standardization of measurement criteria.

Future Directions

We really need to correlate these findings with clinical signs. I would like to perform dynamic MRI studies just to find out if we see any cranial-caudal displacement when the hips are in flexed or extended positions. If we do in fact believe that this could be a clinically significant finding, it begs the question of whether there is a surgical solution for treating lumbosacral pain and thoracolumbar syringomyelia in these dogs. You all would know this better than I do, but it's worth looking into whether potentially going through the transection route of the filum terminale will help alleviate clinical signs in canines. I think this would be very interesting, but getting approval from owners is a different story.

In some other ongoing work, I am trying to correlate MRI findings with clinical signs. So, we have validated questionnaire measures and we are seeing that dogs terminating more caudally are having increased pain and scratching scores. Right now we have a very small sample, so these are obviously not significant findings yet, but we are seeing this trend. We are also doing some sensory threshold testing and we are finding that more caudally-terminating spinal cord Cavaliers have decreased reaction time to algometer testing— they are exhibiting a kind of mechanical hyperesthesia. We will see if this is something worth pursuing in the future, but overall, it is kind of interesting that tethered cord in canines may be another condition that is somewhat translatable to human medicine.

References:

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