Title: Brain Characteristics Noted Prior to and Following Treatment of Deformational Plagiocephaly with a Helmet

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Abstract

A dramatic increase in the number of infants diagnosed with Deformational Plagiocephaly (DP) has been observed worldwide since institution of the American Academy of Pediatrics' Back to Sleep Program.[1-5] According to one published report, the incidence of DP ranges between 3-48%[6]; this translates into120,000-2 million infants/year who develop DP in the United States alone. Some healthcare providers believe that DP is a purely cosmetic condition. This mindset undermines the importance of prevention and correction. In New Zealand, a recent study demonstrated that 39% of children without corrective action had persistent DP at age 3 to 4 years.[7] Additionally, several studies have demonstrated associations between impaired social interactions, developmental problems and DP.[8-13] Thus some researchers now believe that there may be a spectrum of untoward outcomes from brain remodeling resulting from DP [14, 15]. Recent technological advances now allow the detection of diminutive changes in brain structure. In this multidisciplinary descriptive pilot study we will use brain MRI (Magnetic Resonance Imaging) and a cerebral tissue oxygenation monitor, namely Frequency Domain Near Infrared and Diffuse Correlation Spectroscopy (FDNIRS/DCS) to describe if differences in brain structure and characteristics exist in infants with significant DP before and after correction of the deformational defect. This study will enable investigators to seek preliminary evidence that brain development is influenced by the shape of the cranial vault, and that changes in brain structure and characteristics occur with helmet therapy. Additionally this study will help to determine the need for a larger investigation of this phenomenon that would further establish an association between DP and developmental delay.

Team and Resource Description

<u>Study Team</u>
This study will advance the science on DP by utilizing new and innovative non-sedated MRI Imaging procedures (available at Children's Hospital Waltham) to detect problems with infant brain development. Each of the investigators for this study has a clinical practice at BCH and views patient care through a different lens (Neuroradiology, Nursing, Neurosurgery, and Plastic Surgery). It is through our unique perspectives that we have collectively identified a gap in knowledge that needs to be filled and have formed a multidisciplinary cohesive team to do so.

Dr. Michele DeGrazia: This Primary Investigator has experience caring for sick and premature infants with DP. She also serves as the PI on two studies investigating a new positioning device called the cranial cup in effort to prevent/correct positional head shape deformity in a population of Neonatal Intensive Care patients. Dr. DeGrazia's role will be to oversee study operations, including identifying and consenting potential study subjects.

Dr. Ellen Grant: This Co-Primary Investigator is an accomplished researcher. She currently has a number of ongoing investigations examining infants with brain injury of various etiologies using a variety of new technologies including advanced, non-sedated MRI and FDNIR/DCS.

Dr. Mark Proctor,Dr. Alexander Allori, and Dr. Carolyn Rogers: These Co-investigators are accomplished surgeons with firsthand knowledge and experience treating infants with DP and both have published multiple manuscripts on the subject of cranial malformations. They will responsible for identifying and consenting potential study subjects.

Dr. Nadine Gaab: Dr. Gaab is an assistant professor of pediatrics at Harvard University who currently conducts research on developmental cognitive neuroscience within the division of Developmental Medicine at Boston Children's Hospital. Dr. Gaab is experienced with conducting non-sedate MRIs and neurobehavioral assessments on young patients and will assist the research team with the effective implementation of these procedures.

Dr. Maria Franceschini: Dr. Franceschini is an associate professor of radiology at Harvard Medical School and a developer of the FDNIRS/DCS technology. She is a co-investigator and consultant on use of the FDNIRS/DCS technology in this study.

Dr. Kimberlee Gauvreau: This Co-investigator will provide biostatistical support.

Hillary Kuzdeba: Project Manager, will assist with overseeing study operations.

Courtney Porter: Research Coordinator, will assist in facilitating the study by guiding parents through the study trajectory.

Introduction

A dramatic increase in the number of infants diagnosed with DP (Deformational Plagiocephaly) has been observed worldwide since the institution of the American Academy of Pediatrics' Back to Sleep Program.[1, 16] It is estimated that the Neurosurgery and Plastic Surgery departments at Children's Hospital Boston (BCH) care for a minimum 2500 infants per year with positional DP. At present, because DP is considered a purely cosmetic condition, there are limited preventative and corrective resources available to parents and healthcare providers. Additionally, because it is believed to be a benign condition some infants with milder forms of DP may not be recommended for treatment. However, several recent studies have demonstrated associations between developmental problems and DP, leading some to question whether DP causes both skull and brain deformation. [8-13] The purpose of this multidisciplinary descriptive pilot study will be to use brain MRI and a cerebral tissue oxygenation monitor called Frequency Domain Near Infrared and Diffuse Correlation Spectroscopy (FDNIRS/DCS) to describe if differences in brain structure and characteristics exist in infants with significant DP before and after correction of the deformational defect, and to seek preliminary evidence that might link DP with developmental delays.

Background and Significance

<u>Incidence</u>
The rate of Sudden Infant Death Syndrome has significantly declined since implementation of the American Academy of Pediatrics, Back to Sleep Program in 1992 by recommending that infants sleep in the supine position. However with this change in infant sleep position the incidence of DP has dramatically increased [3, 16]. The incidence

of DP ranges between 3-48% (120,000-2 million) for all infants.[6] Infants with DP have irregular or misshapen heads. DP develops as the infant's thin soft skull conforms to the flattened bedding upon which the infant is placed.[7] Issues such as prematurity, lack of full bone mineralization, neurological deficits, preferential head position (torticollis), sedation, paralysis and limited tummy time increase the risk for DP. [5, 8, 17, 18] While it is reported that some milder forms of DP resolve spontaneously, a recent study demonstrates that 39% of children without corrective action had persistent positional head shape deformity at age 3 to 4 years.[7]

Deformational Plagiocephaly in Full Term, Healthy Infants

Brachycephaly is one form of DP. Brachycephaly is reported to result from the infant's head resting on a firm mattress or other solid surface when in the supine position. Common in term infants, this deformation is characterized by occipital flattening (unilateral or bilateral), ear misalignment, frontal bossing, and facial asymmetry.[19] This form of DP has become more prevalent since initiation of the Back to Sleep campaign by the American Academy of Pediatrics (AAP) and other guiding agencies during the 1990's.[5, 6, 19, 20] The Back to Sleep campaign recommends parents place their infants supine to sleep and this change in sleep position has resulted in a dramatic decline in Sudden Infant Death Syndrome.[1]

Plagiocephaly is another common form of DP associated with the supine sleeping position and the Back to Sleep campaign.[20, 21] Plagiocephaly usually results from the head being positioned in the same direction repeatedly and may or may not be related to congenital muscular torticollis.[5, 22] With this type of head shape deformity there is asymmetry of the head shape (one side of the occiput is flattened), and ear misalignment can be present.

Dolichocephaly is a narrow, elongated head shape. This deformation develops when the infant is frequently placed in the prone or sidelying-position and is commonly seen in the premature infant population and rarely observed in full term infants.[18, 23] The actual incidence of dolichocephlay is not known, though infants that are sick or recuperating from illness, and spend more time in their beds in the prone position, are more vulnerable to developing this type of positional head shape deformity.[23]

Social Impact of Deformational Plagiocephaly

The literature is replete with documents to support the claim that the undesirable head shape and facial features associated with DP can lead to problems with parent infant attachment and social isolation as the child grows.[8-11] This is because parents of infants with positional head shape deformities find their infant to be less attractive. In fact, parents are so concerned about DP that a recent search of the Internet revealed a number support groups for parents, allowing them to share their concerns and obtain information about this common problem.[24-27]

Neurodevelopmental Impact of Deformational Plagiocephaly

The cranial vault is made up of several plates of bone that are separated by sutures. The bone plates allow protection for the brain while the sutures allow for expansion and growth of the brain. Brain growth is rapid during the first three years of life. During normal growth it is believed that cells in the dura mater, a lining of the brain respond to brain expansion and influence bone growth.[28] However, it is not known to what extent brain development is impacted when this normal process of brain expansion and bone growth is disrupted.

Much of the work with respect to cranial structure, brain development and developmental delay has involved infants with craniosynostosis.[29] Craniosynostosis is a severe condition that results in inadequate brain growth from premature fusion of one or more sutures of the skull, and requires surgical intervention to prevent long-term untoward neurodevelopment outcomes.[23]

More recently though, some investigators are hypothesizing that DP may cause developmental problems in infants from the abnormal formation of the brain due to impaired expansion and compression from the deformed skull. This hypothesis, developed in response to numerous anecdotal and published reports linking DP (an unintended consequence of the Back to Sleep Program to prevent Sudden Infant Death Syndrome) to gross/fine motor delays, problem solving difficulties, communication deficits, vision/hearing problems and delayed developmental milestones, and has resulted in a broader examination of this phenomenon [7, 20, 21, 30-33], beyond the aesthetics.

In review of the literature, one study of 287 infants with DP, 36% of parents reported that their child had one or more developmental delays such as gross motor delays, problem solving difficulties, and personal-social problems.[7] Similarly, another study comparing toddlers with and without DP showed that toddlers with DP scored lower than demographically similar, but unaffected peers using the Bayley Scales of Infant Development III.[34] Additionally, in 2002, Balan et al demonstrated depressed cortical sound processing, indicative of dysfunction in auditory processing, in a sample of infants with posterior DP when compared to infants without DP.[12] Furthermore, Siatkowski et al in 2005, studying the visual fields of 40 infants with DP found that 35% had constriction of one or both hemifields by at least 20 degrees, suggesting that DP may affect visual field development. However Siatkowski also reported that there was no correlation between laterality of the constriction, to laterality of the asymmetry.[35]

With these mounting concerns over the associations between DP and untoward outcomes, healthcare providers now question the long held belief that DP is a purely cosmetic condition. Some now hypothesize that there may be a spectrum of untoward outcomes that result from brain remodeling and this may depend upon the extent to which the skull is misshapen.[14, 15] Thus investigators are now reevaluating whether or not DP is linked to neurodevelopmental problems.[13]

Technological Advances

Magnetic Resonance Imaging (MRI). MRI offers a safe alternative to other radiologic imaging techniques. This is because MRI uses a strong magnet instead of radiation to make images of the body's interior. The clarity and detail of the pictures from the MRI studies allow for the examination of the human body structures and functions. Therefore in recent years, MRI has become the tool of choice for examining the newborn and infant brain and in this study an MRI of the brain will permit the examination of brain volume, myelination and perfusion. Furthermore newly discovered methods for obtaining sedation free MRI's will be employed by the investigators.

In newborns and infants, MRI is routinely used in the diagnosis and monitoring of conditions such as hypoxic-ischemic injury, brain occupying lesions or neoplasms, stroke, encephalopathy, and white matter injury in preterm infants.[36-47] The typical MRI scan in neonates and infants takes approximately 30-45 minutes. In preparation for the MRI study infants are generally fed, wrapped snuggly, then earmuffs are placed over

their ears to protect them from the tapping sound of the scanner. Some infants also require light sedation to ensure they remain still during the imaging procedure.[36]

The 3 T field strength is reported to be optimal for MRI's of the neonatal and infant brain. A typical MRI sequence may include a volumetric T1-weighted sequence, T2- weighted axial sequence, a susceptibility-weighted image or an axial diffusion sequence with a calculated apparent diffusion coefficient map, and at least 1-2 MR spectroscopy (MRS) samples.[36] Also MRA and MRV may be obtained to look at both the arterial and venous structures respectively.

MRI has been used extensively to diagnose and predict outcomes for infants with hypoxic ischemic encephalopathy and white matter injury of preterm infants. In hypoxic ischemic encephalopathy an array of changes to the brain are observed with MRI and vary according to the timing of the exam. In simple terms, beginning 2-3 days following the injury, T1-weighted images provide information on signal abnormalities or change in the thalamus, putamen, globus pallidi and cortex, while T2-weighted images demonstrate changes to the thalami and basal ganglia after 7 days. In contrast, diffusion weight images are beneficial in examining the neonatal brain for hypoxic injury in the first few days following the injury and will typically show reduced diffusion in the ventrolateral thalmi. MRS is often added to measure lactate, a by-product of tissue injury. In preterm infants MRI is most frequently used to look for white matter injury associated with intraventricular hemorrhage. In this condition high signal intensities are observed on T1-weighted images and hypointense signals are noted on T2 weighted images in the posterior ventricular white matter and frontal white matter.[36] Many studies have linked MRI findings of thalamic and white matter injuries to severe cognitive and motor disabilities supporting the use of MRI for the routine examination of infants with suspected brain injury.[36, 39, 40, 48]

In addition to diagnosing and monitoring conditions such as hypoxic ischemic encephalopathy and white matter injury investigators are now beginning to use MRI to identify relationships to detect brain remodeling. In 2007 Mewes et al, found significant differences in skull shape and brain parenchyma between 20 term and 24 preterm infants. In addition they also found that premature infants exhibited a specific type of non-synostotic DP called dolichocephaly that influenced both subcortical and cortical brain morphology. From these findings, Mewes hypothesized that brain displacement seen on MRI was the result of mechanical forces from the abnormal cranial structure in the cohort of premature infants with dolichocephaly.[49]

In the past, nearly all infants undergoing MRI required sedation and or analgesia, however recent advances in MRI now allow for these studies to be performed without sedation. [50-53] At BCH, there are two quality improvement programs are underway, the Try Without Program designed for children aged 4-6 years and Feed and Wrap Program for infants aged 0-3 months. Both programs have noted promising results. The Try Without Program boasts a success rate of 89.5% (unpublished data) as of May 2010 and the Feed and Wrap Program has been in place for many years with regular reported successes. Moreover, it is with these new programs in mind that researchers are now reconsidering MRI as feasible tool for exploring conditions once thought too risky due to the need for sedation.

Frequency Domain Near Infrared and Diffuse Correlation Spectroscopy (FDNIRS/DCS). Near-Infrared Spectroscopy is an inexpensive bedside tool for evaluating oxy and deoxy-

hemaglobin levels in the brain and can provide important information about brain health.[54] There are many NIRS technologies available for use in pediatric population and these technologies have been extensively examined in the literature. However, for this investigation we have selected to use the FDNIR/DCS system for the purposes of examining cerebral oxygen consumption.

At BCH, bedside FDNIR/DCS has been found to be a reliable measure of cerebral blood flow (CBF_i) and neuronal cerebral oxygen consumption ($rCMRO_2$) when compared to cerebral hemoglobin saturation (SO_2) measures obtained by the more commonly used continuous wave (CW) NIRS systems. For instance in one prior study at MGH, quantitative FDNIRS instrumentation was used to measure neonates with hypoxic ischemic injury and the relative cerebral metabolic rate of oxygen consumption ($rCMRO_2$) was significantly increased in brain-injured infants compared to healthy GA and age matched neonates, whereas SO_2 showed no significant change. [54] Furthermore regional increases in $rCMRO_2$ were observed during development, while rSO_2 showed no significant change.[55]

Additionally, in in one prior study at CHH using the combined FDNIRS/DCS system, significant decreases in CBF_i and $rCMRO_2$ were observed in term infants undergoing hypothermia therapy for clinical hypoxic ischemic brain injury, whereas SO_2 showed no significant change. Furthermore, in a study of premature infants at BWH, FDNIRS/DCS was found to offer a safe and quantitative bedside technique to assess hemodynamic and metabolic parameters, facilitating individual follow-up and inter-subject comparison.[56] Moreover, in premature infants, SO_2 was insensitive to post-menstrual age (PMA), correlating better with hemoglobin concentration in the blood, though CBF_i and $rCMRO_2$ correlated better with PMA. In summary, this work at Harvard hospitals suggests that SO_2 is less sensitive to injury, metabolic suppression with hypothermia, and increasing metabolic demand with development, while $rCMRO_2$ shows significant changes and thus has great potential as a biomarker of brain injury and development. Therefore it is for these reasons that we have selected FDNIRS/DCS system as the tool of choice for measuring cerebral oxygen consumption, a marker of brain health, in this investigation.

Purpose Statement

Some researchers and healthcare providers are concerned that DP may be more problematic than once thought. Concurrently, technological advances now allow researchers to detect diminutive changes in brain structure. In this multidisciplinary descriptive pilot study we will use brain MRI and a cerebral tissue oxygenation monitor to describe if a difference in brain structure and characteristics exist in infants with significant DP before and after correction of the abnormality. Knowledge generated from this study will enable investigators to seek preliminary evidence that brain development is influenced by the shape of the cranial vault, and that changes in brain structure and characteristics occur with helmet therapy. Additionally this study will help to determine the need for a larger investigation of this phenomenon that would further establish an association between DP and developmental delay.

Specific Aims

1. Specific Aim: To describe if differences in brain volume/structure exist by Brain MRI in a sample of infants prior to and following treatment of significant DP with helmet therapy.

2. Specific Aim: To describe if differences in myelination of axonal pathways exist by Brain MRI in a sample of infants prior to and following treatment of significant DP with helmet therapy.

3. Specific Aim: To describe if differences in myelination of axonal pathways exist by Brain MRI in a sample of infants with significant DP compared to infants with similar characteristics but less severe or no DP.

4. Specific Aim: To describe if differences in perfusion of cerebral structures exist by brain MRI in a sample of infants prior to and following treatment of significant DP with helmet therapy.

5. Specific Aim: To describe if differences in cerebral oxygen consumption by Frequency Domain Near Infrared and Diffuse Correlation Spectroscopy (FDNIRS/DCS) exist in a sample of infants prior to and following correction of significant positional head shape deformity

6. Specific Aim: To describe the cognitive ability in five areas of neurobehavioral development in a sample of infants with DP prior to and following helmet treatment using the Mullen Early Scales of Learning (MSEL).

Research Design and Methods

Design: This is a descriptive pilot study.

Setting: Infant participants meeting inclusion and exclusion criteria will be enrolled through the outpatient plagiocephaly clinics (Neurosurgery and Plastic Surgery clinics) at Boston Children's Hospital, Boston Children's Hospital Waltham and Boston Children's Physicians South (Weymouth)

Table 1.

Inclusion Criteria	Exclusion Criteria
- DP requiring helmet therapy -Term gestation at birth (37 weeks or greater) -Less than/or equal to 8 months of age -No history of major health problem such as birth injury, genetic disorder, intracranial hemorrhage, hydrocephalus, neurologic abnormality -No history of implantable metal device or internal/external orthotic device	- DP not requiring helmet therapy -Premature gestation at birth (less than 37 weeks gestation). -Greater than 8 months of age -History of major health problem such as birth injury genetic disorder, intracranial hemorrhage, hydrocephalus, neurologic abnormality -History of implantable metal device or internal/external orthotic device –Infants not completing prescribed treatment for correction with a helmet

Primary Study Sample: We believe that a sample size of 10 subjects meeting the inclusion and exclusion criteria in Table 1., will provide enough information to determine the need for a larger investigation of this phenomenon. To ensure the desired sample size of 10 subjects, a convenience sample of 10-15 infants (that includes 5 additional patients for attrition) with DP, recommended for treatment with helmet therapy, will be recruited into this study.

Comparison Sample: In Aim 2 we will retrospectively identify a sample of infants with similar characteristics (gender, age and race/ethnicity), with a less severe form of DP, or no DP to serve as comparisons.

Staff Education: All research staff will be Citiprogram trained. Also, research staff involved in recruiting, consenting and data collection procedures will receive training by the study PI.

Human Subjects: Prior to initiation of study procedures IRB approval will be obtained. The risk of a serious adverse event is unlikely in this study; however there are other inconveniences and risk to participation to be considered as follows:

Inconvenience: If recruited at Boston Children's Hospital Waltham or Boston Children's Physicians South (Weymouth), study subjects and their parents may be asked to go to Boston Children's Hospital on two separate occasions to complete the cerebral tissue oxygenation monitoring. Parents will be given the option to decline this testing.

All study subjects and parents will be asked to return to BCH Waltham on two separate occasions to have testing that is not part of the routine management for DP with helmet therapy. Parents will not be compensated for their time, the cost of transportation or parking during these visits, and the visits will last approximately 2 ½ hours. In the event that the study team is unable to obtain measures during the scheduled visits due to time limitations, parents will be given the option to schedule additional appointments to complete the measures. There will be no obligation to attend these appointments.

Risk with Brain MRI: MRI is considered a safe FDA approved procedure with no inherent risk to the study subjects; however significant injury can occur to individuals with implantable or external metal devices that undergo MRIs. Therefore, all MRIs will be performed by, appropriately credentialed, BCH personnel. All study subjects will be thoroughly screened to be sure they have no implantable or external metal devices upon enrollment, during consent and prior to each MRI study. Additionally, parents of all study subjects will be asked to change their infant into (hospital or own) attire that is free of metal prior to each MRI study. Furthermore since the Brain MRI requires that the infant remain still for approximately ½ hour, anecdotal evidence suggests there is a 50% chance that a Brain MRI will not be able to be obtained on the first attempt necessitating the need for a repeat visit.

Risk with FDNIRS/DCS: The use of American National Standards Institute (ANSI) and Food and Drug Administration (FDA) approved light levels does not involve any known risk. The laser light used to make the measurements has very low power and is considered to present minimal risk–that is, no more risk than the subject would encounter in everyday life. The light intensity used with this device is many times less

then the amount of near infrared light the subject would receive during an outdoor walk on a sunny day.

The optical probe requires close contact with the skin. It doesn't cause pain or distress. It may cause some minor skin irritation, but this effect is no greater than that encountered from clinical EEG monitoring probes.

Enrollment Procedures: Trained clinical and research staff will screen infants for study eligibility, including MRI eligibility, prior to arrival for their clinic appointments at Boston Children's Hospital, Boston Children's Hospital Waltham, or Boston Children's Physicians South (Weymouth). A recruitment flier will be handed out by clinic administrative staff to families coming in for possible posterior deformation. The flier will provide parents with the opportunity to be aware of the study before being approached by an investigator. The clinical staff will ask parents of the prospective participants who meet eligibility criteria if they are interested in hearing about a research study. Parents who agree to hear about the study will be approached by one of the investigators for consent. The investigator will describe the study in detail and answer any questions. The investigator will also confirm MRI eligibility. Parents of infants who meet study criteria, and who agree to have their infant participate will be asked to sign a consent/HIPPA form. Parents will be provided with a study activity checklist to use as a reference as they progress through the study trajectory. Parents will also be asked to fill out a short demographic survey (ex: infant age, race, known medical conditions) and provide their contact information for follow-up later in the study.

If parents do not want to enroll at the time of their clinic visit but are still interested in possibly participating, the consent team will provide them with a copy of the consent form for them to take home and review, along with the study team member's contact information if the family would like to contact them to enroll or ask questions. In these instances where the family would like some time to make a decision, the consent team will ask the parents if they would be willing to have the team contact them by phone a few days after the clinic visit to check in and learn of their decision to participate. The study team will attempt to contact a family to learn of their decision a maximum of 3 times after the in-person clinic visit. If the team is unable to get in touch with the family after 3 attempts, they will stop trying to contact the family. If parents do not want to be contacted and indicate this to the team, there will be no more contact attempts.

Study Procedures: The treatment of significant cranial asymmetry, with cranial remolding orthosis typically commences as early as possible, usually around 3-6 months of age. Treatment involves a lightweight, plastic and foam orthosis made from a 3-D scan of the infant's head. The plastic and foam orthosis (known as a Helmet therapy) is made of a plastic flexible shell lined with polyethylene foam. The orthosis is modified over time to allow for growth and provide a pathway for the infant's head to grow into a more symmetrical shape.

As part of their routine helmet therapy treatment for DP, study participants will be sent to the NOPCO brace center at BCH or CH Waltham for head shape measures including a laser scan of their head. Participants will also have cerebral tissue oxygenation monitoring completed (FDNIRS/DCS) while waiting for the head shape measures to be obtained or following the measures. If recruited at CH Waltham or Weymouth, parents may be asked to go to BCH for the cerebral tissue oxygenation monitoring at a later

date. Next, arrangements will be made for the study subjects to go to CH Waltham at later date (at a time convenient to the parents and during normal business hours) for MSEL assessment and non-sedated brain MRI. Parents of study subjects will receive instructions on preparation for their day of testing and what they are to expect when they arrive. Parents will be informed that a study team member will be available on the day of the testing and will remain with them throughout the brain MRI. After all initial measures (head shape measures, laser scan, FDNIRS/DCS, MSEL, and Brain MRI) are obtained the study subjects will begin treatment with their helmets. During this time, study subjects will receive routine care and management for correction of the DP, including routine visits with the Neurosurgery or Plastic Surgery clinic physicians, and routine readjustments of their helmets. Upon completion of treatment and resolution of the DP study subjects will have their head shape measures obtained, including a laser scan of their head, cerebral tissue oxygenation monitoring, MSEL and a non-sedated brain MRI. Once again these visits will occur during normal business hours, at a time convenient to the parents. If the subject's routine care and helmet readjustments are taking place at CH Waltham or Weymouth, the subject and their parents may be asked to go to BCH for cerebral tissue oxygenation monitoring. At the end of the second MRI appointment, parents will be offered a CD of their infant's MRI images. These images are not meant for diagnostic purposes and should not be used to inform future treatment decisions for the infant. In the event that the study team is unable to complete the required cerebral oxygen monitoring measures or developmental assessment due to time limitations, parents will be given the option of scheduling additional appointments to complete these measures. There will be no obligation to attend these appointments.

Families who attend/complete both sets of MRI measures (pre and post), will be offered a $50 gift card at the end of the study to offset some of the gas costs incurred driving to the MRI appointments. In instances where families attempt the MRI but the baby cannot be effectively scanned due to movement, the families will still receive their gift card. Families who do not wish to attend the MRI, cancel their MRI appointments without rescheduling, or fail to arrive at their MRI appointments will not be eligible for the gift cards. The gift card may be given to the family at the end of their last MRI appointment if available, or will be mailed to them after they complete the study. If mailed to the family, they will receive a written thank you letter along with the gift card.

Comparison sample: To identify infants with similar characteristics but less severe or no DP, our neuroradiology team members will conduct a retrospective chart review from within BCH medical records. Infants with similar characteristics but with no or less severe DP as measured according to *Cranial Index and Cranial Symmetry Measures (see Head Shape Measures section below)* will be identified as our comparison sample. This will enable us to provide descriptive comparisons of Brain MRI axonal pathway myelination between infants with less severe or no DP.

Study Timeline

This pilot study will take approximately 1.5 years to complete.

Table 2.

Month 1	Month 2-4	Month 2-10	Month 8-10	Month 11+
IRB Application, Approval, Education of	Enrollment, Head Shape Measures	Treatment for DP	Head Shape Measures Brain MRI	Data Analysis &

clinical and study staff	Brain MRI FDNIRS/DCS MSEL		FDNIRS/DCS MSEL	Manuscript Preparation

- Average time for treatment of DP is 4-6 months.

Head Shape Measures

Cranial Index and Cranial Symmetry Measures: To ascertain that correction of the infant's head is achieved routine cranial index and cranial symmetry measures obtained at the NOPCO brace center, will be reviewed by the study team. The cranial index, is an objective measure that quantifies head shape by dividing the head width (M-L) by length (A-P) then multiplying it by 100% [18]. The normal cranial index measurement is between 73%-85% is used to assess for brachycephaly or scaphocephaly. To assess for DP, the right anterior-posterior measures and left anterior-posterior measures will be used. For this measure, an 8mm difference in the right and left anterior-posterior measures will be indicative of asymmetry. In addition, and also as part of their routine care, a licensed orthotist will use a surface laser scanner to secure a computer image of the infant's head. The FastSCAN Handheld Laser Scanner to quickly and conveniently digitize the three-dimensional surface of the infants' head. Scanning involves smoothly sweeping the FastSCAN Wand over the infant in a manner similar to spray painting. An image of the object appears simultaneously on the computer screen. This type of measure, though fairly new, provides great detail, is reported to be nearly 100% accurate when used to make custom helmets and allows for a second set of measurements to be recorded. Measurements including A-P (length), M-L (width), Right anterior-posterior, Left anterior-posterior, and head circumference will be obtained and recorded.

Outcome Measures

Brain Magnetic Resonance Imaging (MRI): Is a routine diagnostic exam that uses a large magnet, radio waves and a computer to produce 2- and 3-dimensional images of the child's brain. This exam is FDA and does not use ionizing radiation (as in xrays) and thus, is a way to better evaluate various parts of the body. Furthermore this type of exam is painless, since the scanner takes pictures without touching the child's body.

In this study MRI structural data will be obtained *without sedation* prior to and following correction of DP in infants <1 year of age using an age-appropriate neuroimaging protocol that has been previously tested and used at BCH (www.babymri.org). This protocol includes intensive familiarization with MRI prior to the actual neuroimaging session, and the collection of whole brain images via MRI. A trained staff member will be on-call for all scan sessions to make this experience as comfortable as possible for infant participants and their families. [57]

The procedure for the brain MRI includes scanning each subject on a 3T Siemens Trio scanner at Boston Children's Hospital's satellite at Waltham at times best matching nap times. Imaging sessions will begin with a 1-hour conditioning session in the Mock scanner. Infants will then be rocked to sleep in the scan room and placed on the table when they fall asleep using the preparation protocol outlined in www.babymri.org where we now have a success rate of ~ 75%.[58] Once asleep in the MR scanner, imaging will be

completed in less than 45 minutes for each subject, and will include the following sequences:

> **3D motion corrected multiecho MPRAGE and 3D T2 SPACE.** These images sequences will be used to perform semi-automatic assessment of regional and global brain volumes using FreeView.
>
> **Diffusion Tensor Imaging (DTI).** DTI (an advanced MRI technique based on detecting properties of free water diffusion) can help evaluate regional and global maturation of white matter. Tractography, a newer DTI method, allows for quantification of entire white matter tracts [using measures such as anisotropy (FA) and mean diffusivity (MD)].[59] Diffusion Toolkit will be used to create the FA and MD maps and Trackvis will be used to create the tractography images.
>
> **Pseudocontinuous arterial spin labeling (PCASL).** PCASL allows for quantitative estimation of both regional and global cerebral perfusion.

MRI:
Cranial index measures will be performed on 3D volumetric reconstructions of the scalp and brain using both 3D images to determine which shows more potential in quantitating interval changes. In addition both 3D T1 and T2 images will be co-registered in FreeView for semi-automatic hemispheric volumetric analysis by a trained research assistant. Lobar parcellation will also be performed.

MD and FA maps will be co-registered to the volumetric data sets with mean values for the regions segmented on the co-registered volumetric data determined. Bilateral projection fiber systems (i.e. axonal pathways) passing through the internal capsule, optic radiations and the arcuate fasciculus will be segmented using standard techniques with MD and FA for each tract determined.

PCASL data sets will be co-registered to the volumetric data sets and mean perfusion values for regions segmented determined.

Frequency Domain Near Infrared and Diffuse Correlation Spectroscopy (FDNIRS/DCS):
FDNIRS/DCS is a non-invasive test that involves holding an optical probe over 7 different locations on the infant's head for 10-15 seconds in each location. Data acquisition with each instrument requires repositioning of the probe due to hair and superficial large vessels to ensure that the measurement is representative of the underlying brain region. Measurement of FDNIRS/DCS may take up to 1 hour.

MRI and FDNIRS Measures: These measures will be quantified according to their respective units of measure and the investigators will prepare a report of the pre and post exam (by FDNIRS/DCS, MRI) findings, and comparing the two.

The Mullen Scales of Early Learning (MSEL):
The Mullen (Scales of Early Learning) provides a profile of cognitive ability in five areas: Gross Motor, Fine Motor, Expressive Language, Receptive Language, and Visual Reception.

This test assesses visual and language abilities at both receptive and expressive levels and provides an integrated framework within which infant development and interactional patterns can be determined. One of the theoretical features underlying the development of the MSEL is the linking of motor equilibration to early visual and language development. Central motor control and mobility have a primary role in the development of skills and abilities in the four cognitive domains of the Mullen Scales: visual reception, fine motor skills, and receptive and expressive language.

The Gross Motor Scale measures central motor control and mobility. The early Gross Motor tasks asses such skills as sitting, creeping, pulling to stand, and walking.

The Visual Reception Scale tests a child's performance in processing visual patterns. The primary ability areas are visual discrimination and visual memory. The tasks present visual information in various forms and patterns, and assess visual processing skills.

The Fine Motor Scale provides a measure of visual-motor ability: It reflects the output side of visual organization. The tasks require visually directed motor planning and involve visual discrimination and motor control.

The Receptive Language Scale measures the child's ability to process linguistic input. The abilities covered in this Scale are auditory comprehension and auditory memory.

The Expressive Language Scale provides a measure of the child's ability to use language productively. The primary areas covered in this Scale are speaking ability and language formation. These tasks also involve auditory comprehension and auditory memory.

MSEL Reliability and Validity

The MSEL has demonstrated positive results with test-retest and inter-rater reliability. In addition, the MSEL is strongly correlated with multiple assessment tools used to assess cognitive ability in the infant population.

Reliability: According to Mullen, the median internal consistency split-half coefficients (Guilford's formula) for the five Mullen scales range from .75 to .83 and for the composite, .91. (2) Test-retest reliability (with a 1- to 2-week interval between tests): for the Gross Motor Scale of the original Mullen scales, the correlation between tests was .96, and the median correlations on the "cognitive" scale were .84 (with a range of .82 to .85) for children ages 1 to 24 months and .76 (with a range of .71 to .79) for children ages 25 to 56 months. (3) Inter-rater reliability: correlations among raters ranged from .91 to .99 for age groups between 1 and 44 months.[64]

Validity: According to Mullen, concurrent validity testing showed the Mullen scales to have stronger correlations with instruments that measured similar skills than those measuring different skills. The correlations of the Mullen "cognitive" scales with the Bayley Mental Development Index (MDI) were higher (.53 to .59) than their correlations with the Bayley Psychomotor Development Index (PDI; .21 to .52). The ELC also was more strongly correlated with the MDI (.70) than with the PDI (.43). Conversely, the Mullen Gross Motor scale was more strongly correlated with the Bayley PDI (.76) than

with the MDI (.30). Similarly, the Mullen Receptive Language scale had a higher correlation with the Preschool Language Assessment Auditory Comprehension (.85) than with Verbal Ability (.72), while the converse was true with the Mullen Expressive Language Scale (.72 for auditory and .80 for verbal). Finally, the Mullen Fine Motor scale was strongly correlated with the Peabody Fine Motor Scale, across four age groups of children between the ages of 6 and 36 months (correlations ranged from .65 to .82). (2) Predictive validity: no information available.[64]

Brain MRI axonal pathway

The identification of the comparison sample will enable us to provide descriptive comparisons of brain MRI axonal pathway myelination between with infants in our primary study sample against those with less severe or no DP.

Using the Cranial Index and Cranial Symmetry Measures, a comparison sample of infants (gender, age and race/ethnicity) with less severe or no DP will be identified by our neuroradiology team members through retrospective chart review from within BCH medical records. Data collection will be limited to Brain MRI and infant characteristics' data that already exists in the medical records. Data including brain MRIs and infant characteristics will be de-identified for storage. Members of the study team will maintain an electronic record of corresponding MRNs in the study log in the event that data verification or additional analyses are needed.

Axonal pathways for infants with DP primary study sample undergoing helmet therapy and those of the comparison sample will be constructed then examined for differences axonal pathways.

Data Management

Data will be managed and stored by the Cardiology Clinical & Research Regulatory Group at BCH. Baseline cranial index and cranial symmetry measurements (obtained manually and by laser scan) for each of the study subjects will be examined by one the investigators (Neurosurgeon or Plastic Surgeon) to confirm correction. Then one of the other investigators (a neuroradiologist with experience in performing FDNIRS/DCS and Brain MRIs) will examine each of the study subjects independently for changes in brain volume/structure, myelination of axonal pathways, perfusion of cerebral structures and cerebral oxygen consumption for changes pre and post correction. FDNIRS/DCS, brain MRI and MSEL data will be stored into a password protected, secure computer.

Data Analysis

The measures will be quantified according to their respective units of measure and the investigators will prepare a report of the pre and post exam (by FDNIRS/DCS, MRI, and MSEL) findings. The report will include case presentations for each of the study subjects and a description of their comparisons, as specified in the aims. A collective presentation of the findings will be prepared using descriptive statistics (mean, median, mode, and frequencies). Tables and bar graphs will also be used to display the results. Also if the data permits, non-parametric tests (signed-rank) will be used to determine if differences are statistically different from zero when examining the paired observations.

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