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Brain Characteristics Noted Prior to and Following Cranial Orthotic Treatment

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Abstract

Objective: This case report aims to assess a potential association between cranial asymmetry, brain deformation, and associated developmental delay. **Study Design:** Two infants born at $\geq$37 weeks pursuing cranial orthotic treatment for severe Deformational Plagiocephaly (DP) (cranial vault asymmetry index >8.75%) underwent developmental assessment using Mullen Scales of Early Learning (MSEL) and non-sedated brain structural and diffusion magnetic resonance imaging (MRI) prior to and following cranial orthotic treatment. **Results:** In both infants with DP, tractography results revealed alterations in the white matter pathways of the brain. Both infants also had low to low/normal visual receptivity and fine motor skills. After cranial orthotic treatment, cranial asymmetry improved but did not completely resolve, tractography demonstrated a change toward normalized white matter pathways, and visual receptivity and fine motor skills improved. **Conclusions:** These preliminary findings suggest a potential link between DP, altered brain structures, and developmental assessment. Further investigation with a larger sample is warranted.

Keywords

infant, MRI, developmental delay, neurodevelopment, diffusion tensor imaging, brain

Introduction

The term "deformational plagiocephaly" (DP) is a broadly accepted term that refers to the range of head shape abnormalities resulting from external forces and not a congenital structural defect. Deformational plagiocephaly occurs as cranial expansion to accommodate brain growth causes the infant's thin soft skull to conform to flattened bedding or other surface upon which the infant is placed.[1] While it is reported that some milder forms of DP resolve spontaneously, it has been demonstrated that 39% of children without corrective action had persistent positional head shape deformity at the age of 3 to 4 years.[2] Cranial deformation can occur in a variety of shapes, such as scaphocephaly (narrow, "boat shaped"), plagiocephaly (oblique or asymmetric), brachycephaly (short and wide), or a combination of those shapes. The most common observed form is plagiocephaly, characterized by unilateral occipital flattening, ipsilateral ear anterior displacement, ipsilateral forehead bossing, and facial asymmetry.

During the last several decades, a dramatic increase in the number of infants diagnosed with DP has been observed worldwide with an incidence as high as 46.7%, or an estimated 2 million infants per year.[3] This increase is reported to be associated with the use of portable car seats as carriers, seating devices for sleep which are popular in daycare settings, and

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implementation of the American Academy of Pediatrics' Back to Sleep Program to avoid Sudden Infant Death Syndrome.[4–6]

A growing body of evidence suggests there are associations between DP and developmental problems.[2,7,8] This has led to questions about whether DP has the potential to cause brain deformation[2,7,9] and a spectrum of developmental problems, or whether it is the developmental delays that predispose certain infants to DP. The potential for the former is concerning because DP has been considered a cosmetic condition, resulting in variability in treatment recommendations without establishing a treatment protocol. Some speculate that underlying developmental delay is a driver of cranial deformation, while others have theorized that the etiology for developmental delay is impaired expansion of the brain due to compression from the deformed skull and surrounding tissues.[7] This hypothesis was developed in response to numerous reports linking DP to gross/fine motor delays, problem solving difficulties, communication deficits, vision/hearing problems, and delayed developmental milestones.[1,2,4,7–11] Studies have demonstrated the association between hearing and vision problems and DP, which have the potential to influence infant development. Decreased cortical sound processing was shown in a sample of infants with posterior DP when compared to infants without DP, which might indicate dysfunction in auditory processing.[10] Furthermore, a study of visual fields in DP found that 35% of the infants had constriction of one or both hemifields by at least 20 degrees, suggesting that DP may also affect visual field development.[11]

Published studies have also reported an association between the flattened head shape and facial features associated with DP and problems of parent-infant attachment and social isolation as the child grows.[1,12] Studies show that infants with DP exhibited cognitive and psychomotor developmental delays,[7] lower language abilities,[7,9] difficulties in personal-social skills,[1] and problem-solving difficulties[1] compared to typically developing control children. Furthermore, a potential association was shown between asymmetry and flattening of brain structures (including greater height and height-width ratio of the cerebellar vermis, shortening and differences in the orientation of the corpus callosum) and worse developmental outcomes.[9]

Research to date on the developmental implications of DP is limited by small sample sizes, lack of quantitative studies, parental reports, and high variability in assessment tools. These mounting concerns challenge long held beliefs that DP is a purely cosmetic condition, leading to the hypothesis that there may be a spectrum of untoward outcomes resulting from brain remodeling that may be dependent upon the location and extent to which the skull is misshapen.[9]

Within the last decade, use of non-sedated brain MRI, development of reliable brain tractography procedures, and validated neurodevelopmental tools have provided the opportunity to examine neural anatomy and developmental status of infants with greater precision.[13] This study investigates the association between DP and developmental delays. Brain MRI tractography and developmental assessments were used in infants with severe DP prior to and following improvement of cranial asymmetry with a cranial orthotic. The aims of this study were to:

1. Describe white matter fiber tract characteristics for infants with severe DP (cranial vault asymmetry index [CVAI] > 8.75%) on brain MRI prior to and following improvement of cranial asymmetry.

2. Explore evidence that might link DP, brain characteristics, and developmental delay using MRI diffusion tensor tractography and Mullen Scales of Early Learning (MSEL) measures prior to and following improvement of cranial asymmetry.

Methods

Subjects: This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Approval to conduct human subjects research from Boston Children's Hospital's Institutional Review Board was received prior to initiation of study procedures. Informed consent was obtained from the parents of the participating infants prior to the study procedures. Ten infants were enrolled through outpatient Plastic Surgery clinics. Subjects were eligible if they pursued cranial orthotic treatment for severe DP (CVAI $\geq$ 8.75%), were born at term gestation ($\geq$37 weeks), were less than/or equal to 8 months of age, were healthy (defined as having no history of major health problems such as birth injury, genetic disorder, intracranial hemorrhage, hydrocephalus, neurologic abnormality), and were free of implantable metal devices or internal/external orthotic devices that would preclude MRI.

Cranial Orthotic Treatment: Eligible subjects underwent cranial molding with an FDA-approved orthotic device (Boston Band™, Boston Brace, Inc.) as part of their routine clinical care. During treatment, the orthosis was modified by a certified orthotist to allow for growth and provide a pathway for the infant's head to develop a more symmetrical shape.

Neuropsychological Assessments: Study subjects underwent developmental assessment using the MSEL prior to and following the cranial orthotic treatment. MSEL assessments were conducted by hospital staff experienced with conducting neurobehavioral assessments on young patients.

MSEL: Subjects received developmental assessments using the MSEL prior to or following the brain MRIs when they were most alert. The MSEL has been demonstrated to have test-retest and inter-rater reliability.[14] Timing of the MSEL was dependent upon the infant's behavioral state, as judged by the research staff upon arrival to the testing site. A profile of cognitive ability was obtained for the following 5 areas: Gross Motor, Fine Motor, Expressive Language, Receptive Language, and Visual Reception. Developmental exam measurements are provided in Tables 1 and 2.

Structural and Diffusion MRI Data Acquisition: MRI data was collected at a 3 T Siemens Trio Tim scanner (32 channel head coil) at Boston Children's Hospital. The data was obtained without sedation prior to and following treatment with a cranial orthotic for the improvement of DP in infants <1 year of age using an age-appropriate, previously tested neuroimaging protocol.[15] Brain MRIs were conducted by a trained staff experienced in working with young children who provided a comfortable experience for infant subjects and their families. Brain MRIs were scheduled at a time when the infants would be most cooperative (for example during nap time). Infants were fed and earmuffs were placed over the infant's ears to protect them from the tapping sound of the scanner. Infants were rocked to sleep in the scan room and then placed on the table.

Table 1. Cranial Measurements.

Cranial measure	Pretreatment	Comments	Post treatment	Comments
Case 1				
Head Circumference	43 cm	Severe occipital flattening, much worse on right, moderate right ear advancement, minor right frontal bossing, no torticollis	48 cm	Asymmetry is approaching normal range
Cranial Index	96%		93.7%	
Cranial Vault Asymmetry Index	10.1%		3.8%	
Case 2				
Head Circumference	44.65 cm	Mild prominence of supraorbital region, left ear very minimally displaced anterior, moderate to severe occipital flattening on left, no torticollis	45.93 cm	Mild residual asymmetry
Cranial Index	96.2%		93.5%	
Cranial Vault Asymmetry Index	9.3%		5.6%	

Table 2. MSEL Developmental Assessment.

MSEL developmental assessment	Pre raw	Pre %ile rank	Descriptive category	Age/months equivalent	Post raw	Post %ile rank	Descriptive category	Age/months equivalent
Case 1: PRE 5 months 7 days; POST 10 months 15 days								
Gross Motor	9	66	Average	6	13	27	Average	10
Visual Reception	5	4	Below Average	3	15	79	Average	12
Fine Motor	6	16	Average*	4	13	50	Average	11
Receptive Language	–	–	N/A**	–	11	27	Average	9
Expressive Language	6	42	Average	5	13	86	Above Average	13***
Case 2: PRE 7 months 13 days; POST 11 months 10 days								
Gross Motor	11	58	Average	8	16	66	Average	13
Visual Reception	8	10	Below Average	6	15	62	Average	12
Fine Motor	8	12	Below Average	6	16	84	Average	14
Receptive Language	10	73	Average	8	15	84	Average	14
Expressive Language	8	42	Average	7	14	88	Above Average	14

* 1% 'ile above cutpoint for below average; ** Only speaks Korean; *** Learning English, Korean, Japanese and Sign Languages

The MRI protocol for the infants included: 1) T1-weighted sequence motion corrected multi-echo magnetization-prepared rapid gradient-echo (MEMPRAGE) sequence with 176 slices acquired in the sagittal plane, voxel size = 1 x 1 x 1 mm^3, repetition time (TR) = 2520 msec, echo time (TE) = 1.74 msec, inversion time (TI) = 1450 msec, flip angle = 7 degrees, field of view (FOV) = 192-220 mm. 2) Spin echo, echo planar diffusion sequence with 40 slices acquired in the axial plane, 30 gradient directions at b values of 1000 sec/mm^2, 10 gradient directions at b=0 sec/mm^2, voxel size = 2 x 2 x 2 mm^3, TR = 3800-8320 msec, TE = 88 msec, FOV = 180-256 mm. MRI analyses were overseen by a board certified neuroradiologist with pediatric expertise.

MRI data pre-processing and analysis: T1 data was visually checked for any artifacts using the Freeview software (surfer.nmr.mgh.harvard.edu). Quality control of the diffusion data was made with the DTI Prep software[16] and also visually using the FSLview software. Gradient volumes with artifacts were removed from the diffusion series and gradient tables were modified accordingly. Data was corrected for eddy current artifacts by using the eddy correct tool of FSL (fsl.fmrib.ox.ac.uk). All 30 gradient volumes, and the b0 images were co-registered to the first b0 volume using affine registration of FSL.[17] White matter tracts were then reconstructed using the DTI imaging model and the interpolated streamline reconstruction algorithm, with an angle threshold of 40 degrees, no fractional anisotropy (FA) threshold, using the Diffusion Toolkit software (trackvis.org/dtk/), a process known as tractography.[18] The resulting tracts were visualized using TrackVis software.[19] Regions-of-interest (ROIs) were placed using color-FA, FA, and apparent diffusion coefficient (ADC) maps and T1-to-b0 anatomical images in order to ensure tract segmentation accuracy. Each tract that was created was also evaluated for anticipated biologically improbable fibers which were manually removed in both subject cases and comparison infants, according to the following criteria: 1) fibers that looped back on themselves, 2) fibers that jumped to a known adjacent pathway, 3) fibers that were too short to form any coherent tract.[20] We investigated potential white matter fiber tract abnormalities in infants with severe DP on the following fiber groups: commissural/interhemispheric corpus callosum fibers, bilateral projection fibers of corticospinal tract (CST) and medial lemniscus (ML), bilateral association fibers of cingulum, as well as bilateral pathways of the dorsal (anterior, long, and

Table 3. Fiber Pathways and Their Functions.

Fiber pathway	Function
Corpus Callosum	Performance IQ, working memory, complex information processing, language processing.
Corticospinal Tract	Cortical control of spinal cord activity such as control of afferent inputs, spinal reflexes and motor neuron activity.
Medial Lemniscus	Somatosensory function, with emphasis on proprioception, touch, and vibration sense.
Dorsal Language Network	Composed of anterior segment (superior longitudinal fasciculus—SLF), long segment (arcuate fasciculus—AF), and posterior segment. While the long segment is considered to be the "direct segment," the anterior and posterior segments are considered to be the "indirect segments." *Direct (Long) segment* = word learning, phonological processing such as automatic repetition, speech processing. *Indirect (Anterior & Posterior) segments* = semantically based language functions such as auditory comprehension and vocalization of semantic content.
Ventral Language Network	Composed of inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF). *IFOF* = reading and writing, semantic processing, semantic working memory. *ILF* = visual information relay, visual object recognition, object representation to lexical labels linking. *UF* = emotional processing, memory, empathy; semantic processing, lexical retrieval, semantic associations, naming of actions, auditory working memory/sound recognition, speech fluency.
Cingulum	Cognitive control, attention and executive function, working memory, language, visuo-spatial function.

posterior segments) and ventral (inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF)) language networks. The functions of the white matter pathways can be seen in Table 3.

Interhemispheric Fibers

Corpus Callosum: The corpus callosum was manually segmented into 5 equal sections between the genu and the splenium (i.e. genu, rostral body, mid body, isthmus/posterior body, splenium) on the mid-sagittal slice of the T1-to-b0 anatomical image and the tracts from each corpus callosum segment were pseudo-colored for clarity. This segmentation allowed visualization of each segment connected to a specific area of the cortex. The segmented regions were visually checked for accuracy and manual editing was performed to clean up the corpus callosum boundaries and the tracts that deviated from the corpus callosum to other tracts such as the IFOF. Exclusion ROIs were placed to remove fibers belonging to the fornix and the CST.[20]

Projection Fibers

CST and ML: 2 ROIs were used to identify descending fibers likely to belong to the CST. The first ROI was placed in the ipsilateral cerebral peduncle, which was identified anatomically on the axial plane on the ADC map by locating the "molar tooth" sign. The second one was placed in the anterior pons which was visualized on the axial plane on the color FA map as blue regions.[21,22] Multiple fibers jumped from CST to the cerebellum during the reconstruction, but as these fibers showed typical morphology for the CST tracts in the brain, we included them in the reconstructed tracts. To identify ML ascending fibers, we used 2 ROIs, the first one was placed posterior to the cerebral peduncle and the second one was placed in the posterior pons which was also visualized on the axial plane on the color FA map as blue regions.[21] CST and ML were reconstructed in both hemispheres.

Intrahemispheric Fibers

Dorsal Language Network (DLN): We used the "3 segment" model proposed by Catani and colleagues[23] to manually segment the anterior, long, and posterior segments of the DLN. To identify the long segment (red), which corresponds to the classical arcuate fasciculus, an ROI was placed at the level of the widest part of the corpus callosum in the axial plane. To create the anterior segment (green), which corresponds to the superior longitudinal fasciculus, an ROI was placed immediately adjacent to the widest part of the corpus callosum on the anterior coronal plane. To create the posterior segment (yellow), an ROI was placed posterior to ROI's for the long and anterior segments in the axial plane.[20,24] All DLN tracts were reconstructed bilaterally.

Ventral Language Network (VLN): To segment the IFOF (red), an ROI was placed in the sagittal plane to identify the main fiber pathway.[20,24] To segment the ILF, an ROI was placed just superior to the tip of the hippocampus in the anterior temporal lobe.[20,24,25] To segment the UF (yellow), an ROI was placed in the anterior temporal lobe in the coronal plane and an exclusion ROI was placed posterior to the curve of the UF in the coronal plane to remove closely passing ILF and IFOF fibers.[20,24,25] All VLN tracts were reconstructed in both hemispheres.

Cingulum: Cingulum fibers were segmented according to the procedure described by Catani and de Schotten.[13] We also added an exclusion mask to remove corpus callosum fibers that run in close proximity to the cingulum.[20] Cingulum tracts were reconstructed in both hemispheres.

Results

Ten infants with DP were enrolled in this study. Of the 10 subjects, 4 of the families withdrew before the first MRI appointment citing competing demands (return to work, transportation issues, and "significant other" objection). An additional 4 subjects had unsuccessful pre-treatment un-sedated MRIs and withdrew following the first appointment- choosing not to make a second attempt. Two infants completed all of the study requirements including pre and post cranial orthotic treatment MRIs and developmental exams.

Case 1: the child was a healthy female who was 5 months and 7 days old at the time of MRI. She presented to the Plastic surgery clinic for management of right-sided occipital flattening (with no torticollis) first recognized by her parents at 2 months of age. According to her parents, the infant slept

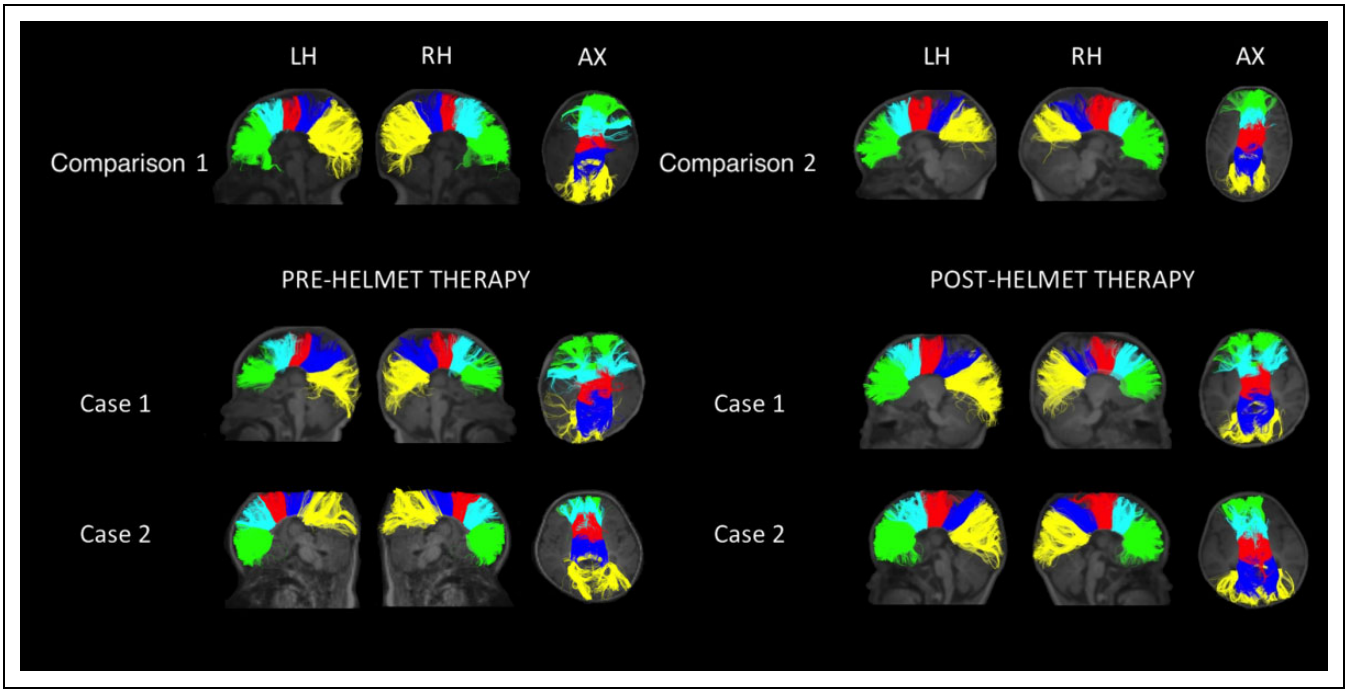

Figure 1. Corpus Callosum. The pseudocolored fibers are overlaid on each infant's own structural MPRAGE image. Five corpus callosum segments are of equal length where Green = genu; Light Blue = rostral body; Red = mid body; Dark Blue = isthmus/posterior body; Yellow = splenium. In the axial view right = right, left = left.

primarily on her back, and resisted "tummy time." Despite their best efforts with repositioning procedures, little improvements had been observed. The child's cephalic index was 96% and cranial vault asymmetry index was 10.1% before the treatment. The infant underwent 4 months of treatment with a cranial orthotic. At the beginning of treatment, the child could not be assessed for receptive language, as she only knew Korean. However, by the end of the treatment the child was learning to speak English, Korean, Japanese, and sign language. Upon completing treatment, the child was 10 months and 15 days old.

Case 2: the child was a healthy female who was 7 months and 13 days old at the time of MRI. She presented to the outpatient clinic with left sided occipital flattening, first observed at 4 months of age. According to her parents, the infant slept in a rocking chair until she was 3 months of age. Furthermore, the parents had reported that despite the use of repositioning techniques and "tummy time," the head flattening persisted. The child's physical exam revealed that she was able to sit without assistance and could roll over. Before the treatment her cephalic index was 96.2% and cranial vault asymmetry index was 9.3%. Upon completing treatment with the cranial orthotic the child was 11 months and 11 days old.

Comparison data: Brain MRI data from 2 age- and gender-matched infants with less severe DP were retrospectively collected for comparison. These comparison examples have been included to show the brain white matter tract formation for infants with mild versus severe (Case 1 and 2) deformational plagiocephaly.

Comparison 1: the child was a healthy female, with mild plagiocephaly. She was 6 months and 26 days old at the time of MRI. Her cephalic index was 83% and cranial vault asymmetry index was 5.4% as measured from her MRI.

Comparison 2: the child was a healthy female with mild dolichocephaly. She was 9 months and 28 days old at the time of MRI. Her cephalic index was 73.2% and cranial vault asymmetry index was 2.6% as measured from her MRI.

MSEL Results: Case 1 demonstrated below average visual reception and low average fine motor skills via exam during the pre-cranial orthotic treatment assessment, and average visual reception and fine motor skills via the post-cranial orthotic treatment assessment (Table 1). Case 2 demonstrated below average visual reception and fine motor skills on the pre-treatment assessment, and average visual reception and fine motor skills on the post-treatment assessment (Table 2).

Tractography Results

Corpus Callosum: Case 1 pre-cranial orthotic treatment tract reconstructions revealed distortion of the 5 segments of the corpus callosum, especially the splenium compared to the corpus callosum of Comparison 1. The post-treatment tract reconstruction revealed more concise divisions of the colored segments of the corpus callosum. Similar to Case 1, the pre-cranial orthotic treatment tract reconstructions in Case 2 revealed distortion within the 5 segments of the corpus callosum, particularly in the splenium of the corpus callosum when

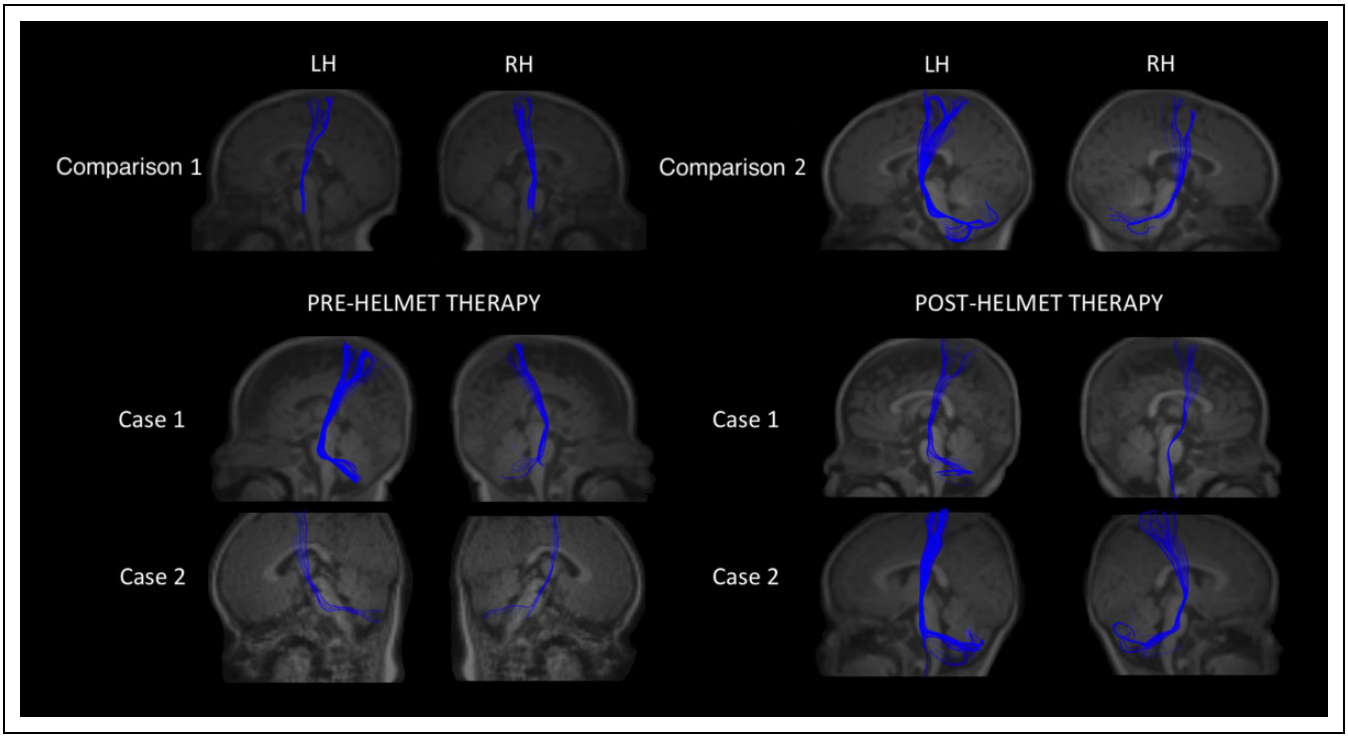

Figure 2. Corticospinal Tract (CST). The pseudocolored fibers are overlaid on each infant's own structural MPRAGE image.

compared to Comparison 1. There was visible improvement in the corpus callosum of Case 2 post-treatment which was comparable to Comparison 2 (Figure 1).

CST and ML: During CST and ML reconstruction in both cases and comparison infants, we noted many fibers deviated from the inferior CST to the cerebellum. These fibers showed typical CST morphology and because of that were included in the following qualitative analysis. Case 1 pre- and post- cranial orthotic treatment CST reconstruction showed an intact tract when compared to the CST of the comparison infants (Figure 2). Case 2 pre- cranial orthotic treatment CST was thinner than the CST of Comparison 1, however, Case 2 post- cranial orthotic treatment CST was similar to the CST of Comparison 2. As for ML tract reconstruction, there were no significant differences between tracts pre- and post- cranial orthotic treatment for Case 1 and 2. However, Comparison 1 ML was thinner compared to the ML of the both Cases at pre cranial orthotic treatment time point (Figure 3).

Dorsal Language Network: Case 1 pre-cranial orthotic treatment DLN reconstructions revealed the anterior and posterior segments but not the long segment of the DLN in the left hemisphere. Furthermore, both segments showed an unusual shape. All 3 segments were revealed in the right hemisphere but their configuration was also unusual compared to Comparison 1. Post-treatment revealed exactly the same segments on both hemispheres, where the shape was clearly improved and more consistent with Comparison 2. Pre-cranial orthotic treatment for Case 2 showed an abnormally configured DLN in both hemispheres compared to the Comparison 1 and the long segment was missing bilaterally. Post-treatment showed a slight improvement in the configuration of the 2 segments. Comparison 1 and Comparison 2 both had all 3 segments revealed bilaterally which all had a typical configuration (Figure 4).

Ventral Language Network: Case 1 pre-cranial orthotic treatment VLN tract reconstructions were all skewed on the side of the flattening, furthermore, the IFOF was sparser than those of Comparison 1. VLN white matter followed a more normalized tract pattern on the contralateral side as compared to the Comparison 1. Post-treatment white matter VLN fiber tracts of Case 1 were more symmetric between the 2 hemispheres but IFOF was still less compact bilaterally compared to the IFOF of Comparison 2. Case 2 pre- cranial orthotic treatment VLN tract reconstructions showed a correctly constructed UF bilaterally, however, IFOF and ILF both followed an abnormal trajectory. The post-treatment white matter VLN fiber tracts for IFOF and ILF of Case 2 followed a more normalized tract pattern but still were more diffuse in appearance than in Comparison 2. Both Comparison 1 and Comparison 2 showed typical reconstruction of the VLN bilaterally (Figure 5).

Cingulum: We were able to construct the dorsal sections[26] of the cingulum well in each dataset; however, it was not possible to reconstruct the parahippocampal (i.e ventral) section[26] of the cingulum in both hemispheres of Comparison 1 and Case 1. Case 1 pre- and post-cranial orthotic treatment cingulum reconstructions were comparable to the Comparisons. Case 2 pre-cranial orthotic treatment showed a clear abnormality in the shape and trajectory of the whole cingulum, especially in

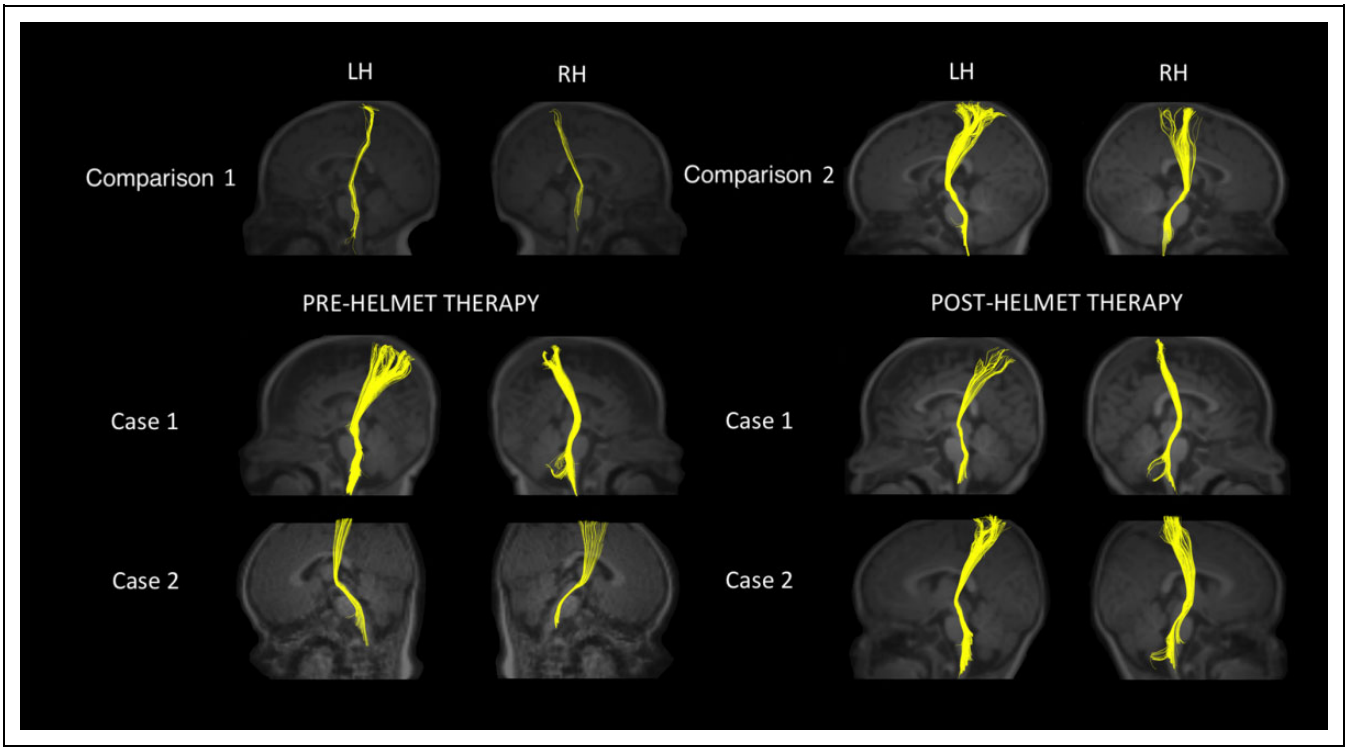

Figure 3. Medial Lemniscus (ML). The pseudocolored fibers are overlaid on each infant's own structural MPRAGE image.

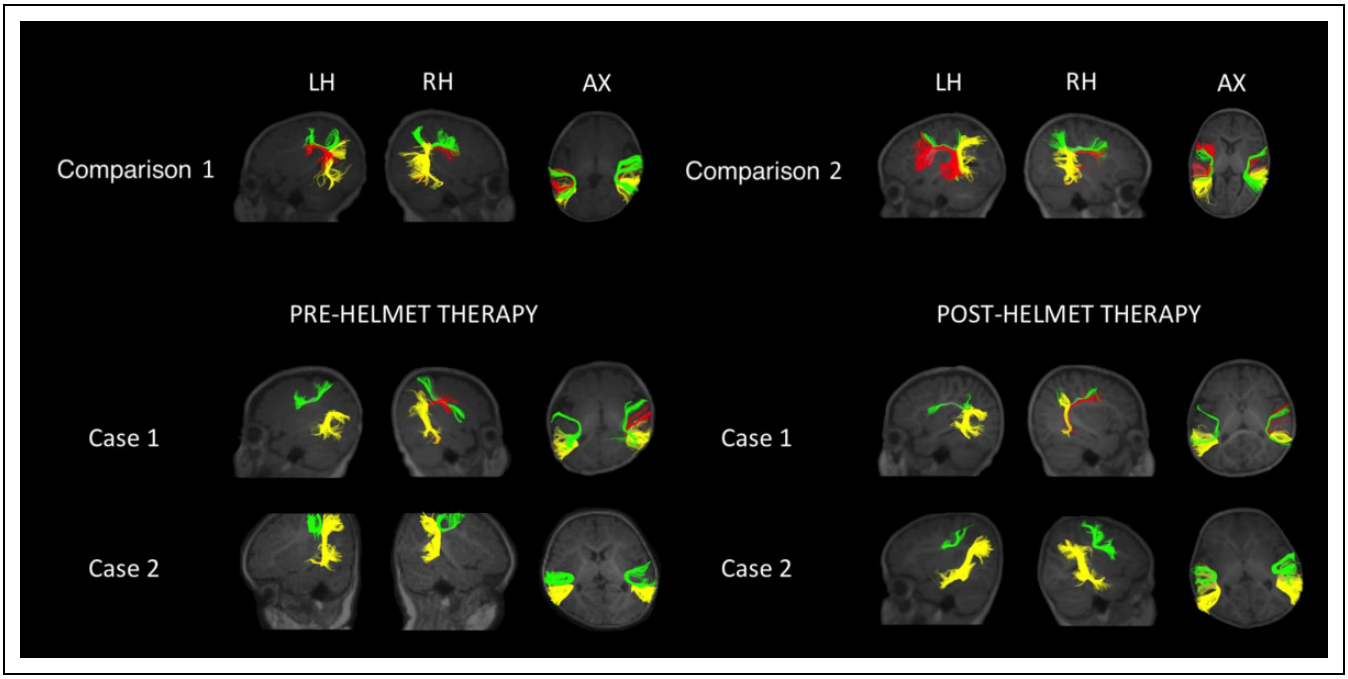

Figure 4. Dorsal Language Network (DLN). The pseudocolored fibers are overlaid on each infant's own structural MPRAGE image. Green = anterior segment of the DLN; Red = long segment of the DLN; Yellow = posterior segment of the DLN. In the axial view right = right, left = left.

the right hemisphere compared to Comparison 1. Post-treatment of Case 2 showed clear improvement in the tracts of the whole cingulum bilaterally and was comparable to the cingulum of the Comparison 2 (Figure 6).

Discussion

Technological advances of the last 2 decades have led to the development and reliable use of fetal and infant brain

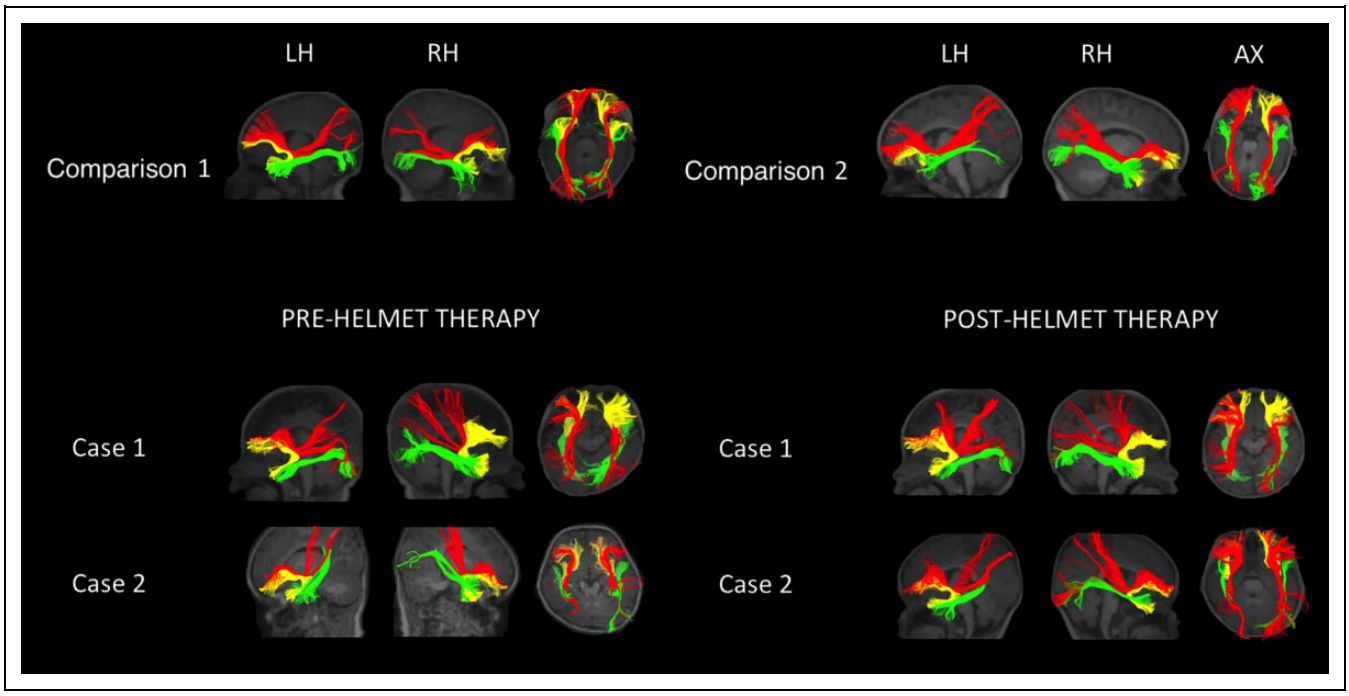

Figure 5. Ventral Language Network (VLN). The pseudocolored fibers are overlaid on each infant's own structural MPRAGE image. Green = inferior longitudinal fasciculus (ILF); Red = inferior fronto-occipital fasciculus (IFOF); Yellow = uncinate fasciculus (UF). In the axial view right = right, left = left.

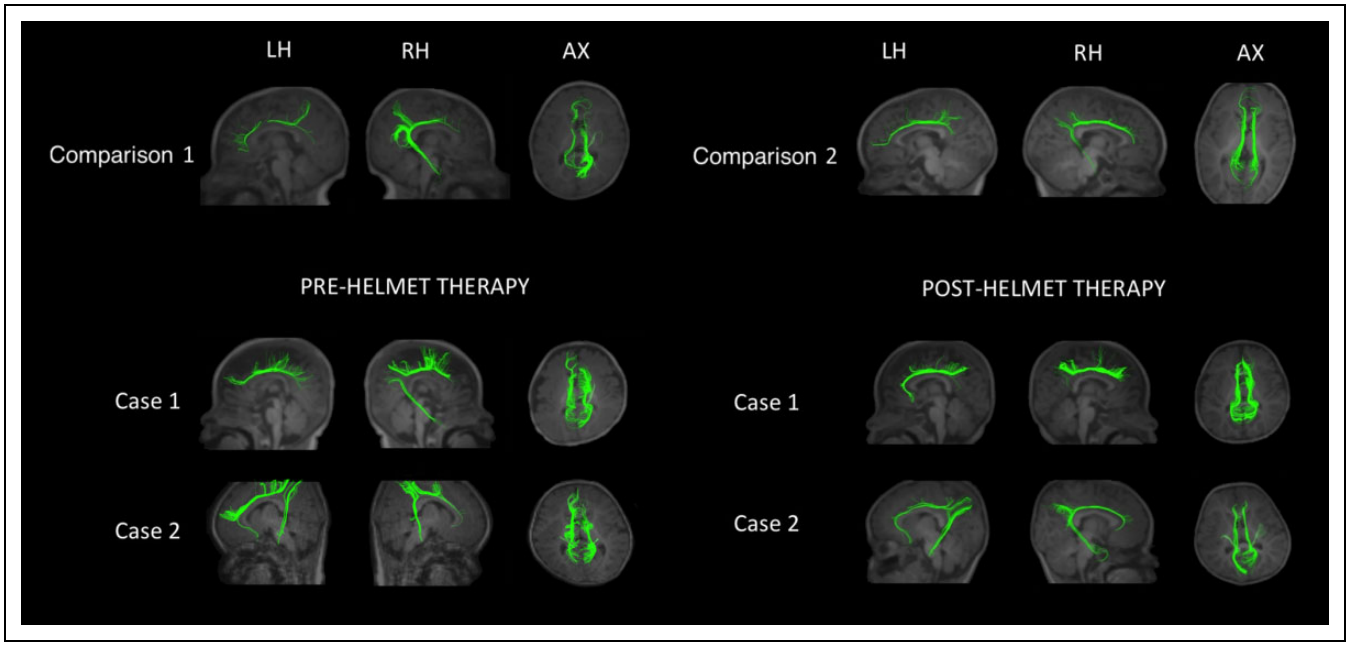

Figure 6. Cingulum. The pseudocolored fibers are overlaid on each infant's own structural MPRAGE image. In the axial view right = right, left = left.

tractography. These efforts provide investigators with a dynamic and standardized process of assessing white matter fiber tract organization and development. Due to the painstakingly detailed documentation of tract anatomy, this provides opportunities to establish linkages between subject history, clinical presentation, and brain white matter tract characteristics.[27] Findings from our study suggest that severe DP may be associated with deformation of brain white matter tracts corresponding to the shape of the overlying deformed cranium. It is also possible that improvement of the plagiocephaly helps to normalize their trajectories.

To our knowledge, this is the first prospective study of white matter fiber tracts in infants with DP. We followed 2 subjects

through the treatment course and collected pre and post-cranial orthotic treatment brain MRI and developmental exam data and compared their major white matter pathways to age- and gender-matched infants. We sought to increase our understanding of the relationship between DP and developmental impairment that has been reported in the literature. Our analyses focused on the corpus callosum, cingulum, DLN tracts (i.e. anterior, long, posterior segments), VLN tracts (i.e. IFOF, ILF, UF), CST, and ML. These tracts have been areas of interest when examining attention and executive functions, memory, sensory, motor, and language pathways of infant brains, and are important to typical neurodevelopment[28] (Table 3).

Our 2 subjects presented with severe DP, one right sided and the other left sided. Pre- cranial orthotic treatment brain MRI tractography displayed alterations to the splenium of the corpus callosum, the cingulum, long segment of the DLN, IFOF of the VLN, and CST tracts for both infants with DP compared to age- and gender-matched infants, as well as low to low/normal visual reception, and fine motor skills via developmental exams. Following substantial improvement of head shape, both infants exhibited normalizing patterns of white matter tracts, and improved visual reception and fine motor skills. These findings align with those of Collett and colleagues who found infants with DP had developmental delay, specifically in the visual receptive and fine motor subscales of the BSID III. However, Collett et al also observed persistent delays in language and cognition subscales at 7, 18, and 36 months using the BSID III.[7,9]

The observed alignment between pre-cranial orthotic treatment brain MRI changes and developmental exam findings in the present study, along with relative post- cranial orthotic treatment improvements observed on MRI and developmental exams, raise important questions about the: 1. influence of cranial deformation on brain development, 2. physiologic and functional consequences of directional head growth due to environmental restrictions, 3. plasticity of the brain as it relates to improvement in head shape, and 4. developmental implication of DP. While we are not the first to raise these questions, our findings viewed within the context of what is known about DP provide a compelling case for further exploration. It is our suspicion that DP may be associated with a spectrum of possible developmental abnormalities, however, our data is too anecdotal to reach any actionable conclusions. It is possible that we observed abnormal trajectories for some pathways, such as the IFOF, because the abnormal head shape made it difficult for the algorithm to accurately reconstruct its course. Additionally, there were 2 abnormal tracts (long segment of DLN and IFOF) without seemingly corresponding abnormalities in behavioral test results, specifically expressive and receptive language subscales of MSEL. Assessment of these language skills at such early ages is challenging and rudimentary in infants. It is hard to know at this very preliminary point in time with only 2 subjects how affected the tracts would need to be before a functional impact is observed.

We do not recommend changes in current management of DP based on these findings and are not advocating cranial orthotic treatment as a management strategy for developmental delay; nor do we assert that the cranial orthotic treatment was directly related to improvements in the white matter pathways or developmental exams observed. To confidently know that improvement of cranial deformities leads to better outcomes a much larger prospective study would be needed. We encourage our colleagues to provide additional scientific evidence to support or refute the associations between DP, brain MRI changes, and development.

Our study had a number of challenges and limitations that prevented us from establishing any firm associations, relationships, and conclusions, and may prevent our findings from being reproducible in a larger study. Most notably we only had 2 complete subject datasets, and MRI data only from 2 age- and gender- matched infants to analyze. Due to the small sample size, we could not perform statistics on the diffusivity values of the white matter tracts that we constructed. Our findings may have been fairly different, including quantitative information about the microstructure of the white matter tracts, if all 10 subjects had completed the study. It is possible, though unlikely, that both children in this study had an undiagnosed condition that could account for the brain MRI tractography changes and developmental exam findings. Additionally, as with all non-sedated brain MRI studies, the methods used to resolve issues with motion artifact, despite carefully performed, could have impacted our findings. Furthermore, we only enrolled infants presenting with plagiocephaly seeking treatment using a cranial orthotic and did not enroll subjects without plagiocephaly, with alternate forms of cranial deformation (such as symmetric brachycephaly), or those with DP treated conservatively. A much larger study of infants inclusive of infants with no DP and varying types and severities of DP is needed to achieve a more complete understanding of the significance of this condition.

Conclusions

This report presents brain MRI findings and developmental exams for 2 healthy term born infants treated with severe DP prior to and following improvement of asymmetry with a cranial orthosis. Using tractography, pre-cranial orthotic treatment brain MRI findings demonstrated altered organization of the corpus callosum, the cingulum, long segment of the DLN, IFOF of the VLN, and CST tracts, and the MSEL physical exam findings were consistent with low to low/normal visual receptivity and fine motor skills. Post-treatment brain MRI findings demonstrated normalization of these white matter pathways, and physical exam findings showed normal visual receptivity and fine motor skills.

These preliminary findings suggest a potential link between DP, changes in brain structures, and developmental exams that could have implications for long-term infant development. Provider recommendations for DP prevention and treatment, and development and interpretation of standardized infant tractography warrant further investigation with a larger sample of infants. Until further evidence is available, caution should be exercised in the interpretation of these findings.

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Author Contribution

Michele DeGrazia and Banu Ahtam contributed equally as first authors.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. DeGrazia is the inventor of a novel device to prevent deformational plagiocephaly in premature infants. Boston Children's Hospital (BCH) and Plagio LLC partially funded past research conducted by Dr. DeGrazia for studies examining deformational plagiocephaly prevention devices, including the device she invented. Plagio LLC in coordination with her employer BCH filed a patent for the device invented by Dr. DeGrazia. Plagio LLC is an affiliate of Boston Brace where subjects received treatment during the study and where some data was collected. Dr. DeGrazia, Plagio LLC and BCH may one day receive royalties for sale of the device by Dandle Lion Medical. Dr. DeGrazia served as an unpaid consultant for Dandle Lion Medical. As of June 2020 Dr. DeGrazia received Plagio LLC shares in the amount of 10%. However, Dr. DeGrazia's device for which she may one day receive royalties was not used in this research. Dr. Banu Ahtam does not have any declarations to report. Dr. Carolyn R. Rogers-Vizena does not have any declarations to report. Dr. Mark Proctor does not have any declarations to report. Ms. Courtney Porter does not have any declarations to report. Ms. Rutvi Vyas does not have any declarations to report. Dr. Cynthia T. Laurentys does not have any declarations to report. Ms. Emily Bergling does not have any declarations to report. Dr. Kara McLaughlin does not have any declarations to report. Dr. Patricia Ellen Grant does not have any declarations to report.

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