Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Early prediction of unilateral cerebral palsy in infants at risk: MRI versus the hand assessment for infants

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BACKGROUND: Neonates with unilateral perinatal brain injury (UPBI) are at risk for developing unilateral spastic cerebral palsy (USCP). This study compares several predictors for USCP later in life.

METHODS: Twenty-one preterm and 24 term born infants with UPBI were included, with an MRI scan including diffusion tensor imaging (DTI) performed at term equivalent age or around 3 months after birth, respectively. T2-weighted images and DTI-based tractography were used to measure the surface area, diameter, and fractional anisotropy (FA) of both corticospinal tracts (CSTs). The hand assessment for infants (HAI) was performed before 5, between 5 and 8 and between 8 and 12 months of (corrected) age. Asymmetry indices were derived from all techniques and related to USCP at ≥2 years of age.

RESULTS: MRI measures and HAI scores were significantly lower for the affected compared to the unaffected side. Before 5 months of age, FA asymmetry on DTI yielded the highest area under the curve compared to conventional MRI and HAI.

CONCLUSIONS: Prediction of USCP after UPBI is reliable using asymmetry of the CST on MRI, as well as clinical hand assessment. Before 5 months of age, DTI tractography provides strongest predictive information, while HAI specifically aids to prognosis of USCP at later age points.

Pediatric Research (2020) 87:932–939; https://doi.org/10.1038/s41390-019-0664-5

INTRODUCTION

Unilateral perinatal brain injury (UPBI) is commonly diagnosed in newborn infants, but the type of injury varies with gestational age (GA). In term born neonates, perinatal arterial ischemic stroke (PAIS) is the most frequent form of UPBI, which is the result of focal disruption in arterial cerebral blood flow.[1,2] In preterm neonates, periventricular hemorrhagic infarction (PVHI) is the most common unilateral brain lesion, which results from impaired venous drainage of the vulnerable medullary veins in the germinal matrix.[3,4]

UPBI may lead to adverse neurodevelopmental outcome, including unilateral spastic cerebral palsy (USCP). Several studies showed that 30–50% of infants with PAIS and around 28–47% of preterm infants with PVHI developed USCP, which is mainly dependent on the extent of the lesion and (secondary) tissue involvement.[5,6] Although no interventions specifically aim to treat UPBI and prevent the development of USCP, new therapies that target neuroprotection or neuroregeneration are on its way.[7,8] Other early intervention programmes include constraint-induced movement therapy, which is specifically developed for patients at risk for developing USCP.[9] These intervention strategies should be initiated as early as possible, when plasticity of the developing brain is highest. To start therapy as early as possible, early identification of those at risk for developing USCP is required.

Magnetic resonance imaging (MRI) is a reliable technique for early diagnosis and prediction of motor outcome after UPBI,[4,5,10] both in the acute phase as well as on follow-up. On follow-up scans, degeneration of axons in the corticospinal tracts (CSTs), known as Wallerian degeneration, is associated with the development of USCP.[5,11–13] However, most studies have used a qualitative evaluation of CST involvement on MRI, while objective quantitative measures of Wallerian degeneration are preferable to increase clinical use. Kirton et al. has demonstrated a quantitative measure of Wallerian degeneration at the level of the cerebral peduncle that corresponds to adverse motor outcome.[14] Diffusion tensor imaging (DTI) can be used to reconstruct white matter fiber tracts, such as the CST, in vivo and allow for quantitative measurement of diffusion parameters in these tracts.[15] DTI tractography offers more detailed information on brain connectivity compared to conventional MRI, is able to provide a quantitative measure of white matter integrity, and can therefore aid in early prognosis of USCP in infants with UPBI.[15–18]

In the literature, a combination of neuroimaging and standardized clinical assessments is recommended for most reliable prediction of USCP at an early age.[19] A relatively new instrument that may contribute to diagnosing motor impairment in young children is the hand assessment for infants (HAI).[20] The HAI scores the function of both hands separately in play-related tasks and provides a scale of asymmetry between hands. The HAI is a non-invasive clinical test that can be performed at multiple timepoints from 3 to 12 months of age.[20] This makes HAI suitable to quantify the development of asymmetric hand function early in life, although its predictive ability compared to early neuroimaging is unknown.

In this study, we aim to investigate the predictive value of several quantitative asymmetry indices (AIs) based on conventional

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Received: 19 April 2019 Revised: 16 September 2019 Accepted: 1 October 2019
Published online: 13 November 2019

MRI, DTI, and HAI in infants with UPBI to predict USCP later in life. As many studies have described the predictive value of one measure to predict USCP, this study specifically aims at comparing several quantitative asymmetry measures in a large group of infants specifically at risk for unilateral CP, additionally studying whether these prediction measures differ between term and preterm infants with UPBI.

METHODS

Patients

For this study, we selected all infants with UPBI on their neonatal MRI, who were born between August 2011 and May 2016 and underwent HAI assessment in the Wilhelmina Children's Hospital in Utrecht, the Netherlands at some point during their first year of life. Parents signed informed consent for the use of their child's data for research purposes. A waiver of authorization to conduct this study was approved by the Medical Ethical Committee Utrecht because HAI assessment and MRI (including DTI) are considered standard medical care for infants with UPBI who were considered at high risk of UCP (WAG/th/14/038370).

Clinical and obstetric characteristics were obtained from the infants' charts (Table 1). Prematurity was defined as infants born before 37 weeks of gestation. Infants had their early MRI when they were admitted to the neonatal intensive care unit (NICU) at the Wilhelmina Children's Hospital (Utrecht, The Netherlands) and as soon as they were stable enough for transportation to the MRI scanner. A follow-up MRI was obtained several weeks later, which corresponded to term equivalent age (TEA) in preterm infants and 3 months postnatal age in term infants. Based on previous research in term and preterm neonates, the follow-up scan was chosen as optimal timepoint for MRI measurements and DTI tractography.[16,21] MRI measurements used in this study therefore refer to the follow-up MRI scan.

Table 1. Patients characteristics.

	Total ($n = 45$)	Term ($n = 24$)	Preterm ($n = 21$)
Male	27 (60.0%)	14 (58.3%)	13 (61.9%)
Gestational age (weeks)*	34.5 (±6.1)	39.5 (±1.5)	28.7 (±3.7)
Birth weight*	2308 (±1153)	3191 (±555)	1299 (±753)
Diagnosis*			
PAIS	18 (40.0%)	15 (62.5%)	3 (14.3%)
PVHI	18 (40.0%)	2 (8.3%)	16 (76.2%)
Other	9 (20.0%)	7 (29.2%)	2 (9.5%)
(Sub)clinical seizures*	22 (48.9%)	18 (75.0%)	4 (19.0%)
Follow-up MRI available	40 (88.8%)	20 (83.3%)	20 (95.2%)
Age at follow-up MRI			
Postmenstrual age (weeks)	47.9 (±5.8)	53.0 (±1.6)	42.9 (±3.7)
Postnatal age (days)	97.1 (±19.3)	93.4 (±14.2)	100.8 (±23.0)
Good-quality follow-up DTI	37 (82.2%)	19 (79.2%)	18 (85.7%)
Corrected age at HAI (weeks)			
<5 months ($n = 44$)	14.9 (±2.2)	14.5 (±2.5)	15.3 (±1.8)
5–8 months ($n = 32$)	28.1 (±2.9)	27.0 (±2.3)	29.5 (±3.1)
>8 months ($n = 32$)	42.1 (±5.1)	42.4 (±6.0)	41.9 (±4.1)
USCP	27 (60.0%)	12 (50.0%)	15 (71.4%)
GMFCS grade I	18 (66.7%)	8 (66.7%)	10 (66.7%)
GMFCS grade II	4 (14.8%)	2 (16.6%)	2 (13.3%)
GMFCS grade III	1 (3.7%)	0 (0%)	1 (6.7%)

Data are given as number (percentage) or mean (±standard deviation)
PAIS perinatal arterial ischemic stroke, *PVHI* periventricular hemorrhagic infarction, *MRI* magnetic resonance imaging, *DTI* diffusion tensor imaging, *HAI* hand assessment for infants, *USCP* unilateral spastic cerebral palsy, *GMFCS* Gross Motor Function Classification System
*Significant difference between term and preterm infants, $p < 0.05$

Imaging methods

MRI was performed on either a 1.5 or 3 T Philips Achieva MR system (Philips Medical Systems, Best, Netherlands) equipped with a 8-channel SENSE head coil and included both conventional MRI and DTI sequences. The conventional axial or coronal MR protocol consisted of at least a T1-weighted imaging (T1WI), T2WI, and diffusion-weighted imaging (DWI), of which the scanning protocol details have previously been reported.[22]

Single-shot echo planar DTI was acquired in either 32 or 45 noncollinear directions with one of the following scanning protocols; 1.5 T, 32 directions: repetition time (TR): 6817 ms, echo time (TE) = 87 ms, voxel size = $1.98 \times 1.98 \times 2$ mm^3, *b* value 800 s/mm^2, SENSE factor of 2.5. On 3 T, 32 directions: TR: 5685 ms, TE = 70 ms, voxel size = $1.41 \times 1.41 \times 2$ mm^3, *b* value 800 s/mm^2, SENSE factor of 2. 3 T, 45 directions: TR: 6.500 ms, TE = 80 ms, voxel size = $2 \times 2 \times 2$ mm^3, *b* value 800 s/mm^2, SENSE factor of 1.4.

Intensive care was continued throughout the examination with the attendance of a neonatologist or physician assistant, and the heart rate and transcutaneous oxygen saturation were monitored by pulse oximetry in all infants (Nonin, Minneapolis, MN) as well as respiration rate (Philips ACS-NT, Best, The Netherlands) A vacuum pillow (Med-Tec, Orange City, IA) was used to prevent head movement. Minimuffs (Natus Medical, San Carlos, CA) were used for hearing protection. Preterm infants at TEA were sedated using oral chloralhydrate 50–60 mg/kg, according to clinical protocol. At 3 months after birth, the term infants were sedated throughout the examination with an intramuscular injection of 0.1 ml/kg of a combination of pethidine (2 mg/kg body weight), chlorpromazine (0.5 mg/kg body weight), and promethazine (0.5 mg/kg).

Conventional MRI analysis

Using T2-weighted images, brain stem sections were analyzed using a previously described technique.[14] When T2WI were unavailable, T1WI or inverse recovery T1WI images were used. Asymmetry of the cerebral peduncle diameter and surface area was used as a proxy of CST asymmetry. A first line was drawn parallel to the fronto-medial part of each peduncle, toward the midbrain (Fig. 1a, line AB). A second line (Fig. 1a, line BC) was drawn perpendicular to this line, crossing the peduncle. The area fronto-lateral to this line was considered to be the two-dimensional surface area of the cerebral peduncle (Fig. 1b) Finally, a third line was drawn, parallel to line BC at the broadest part of the peduncle (line D), reflecting the width of the peduncle (Fig. 1a). Inter-rater reliability was determined between two researchers by repeating volume and diameter measurements of both cerebral peduncles in 15 infants.

DTI analysis

DTI data were processed with ExploreDTI.[23] The DWIs were realigned to the b0 image to correct for subject motion and eddy current–induced geometric distortions. In this process, the diffusion tensor was fitted for each voxel after adjusting the diffusion gradients for the *b*-matrix rotation.[24] Furthermore, the DTI data were registered to a single-subject neonatal DTI template (freely available http://cmrm.med.jhmi.edu), using a rigid registration method, to correct for any angulation asymmetries. A quality check was performed using the outlier profile. DWIs with >0.5% outliers were discarded; and if the number of discarded DWIs exceeded 10% of the total number of images (32 or 45), the whole DTI scan was excluded from further analyses. Whole-brain tractography was performed, using a 1-mm step size.[25] Propagation of the fibers was stopped if a voxel with a fractional

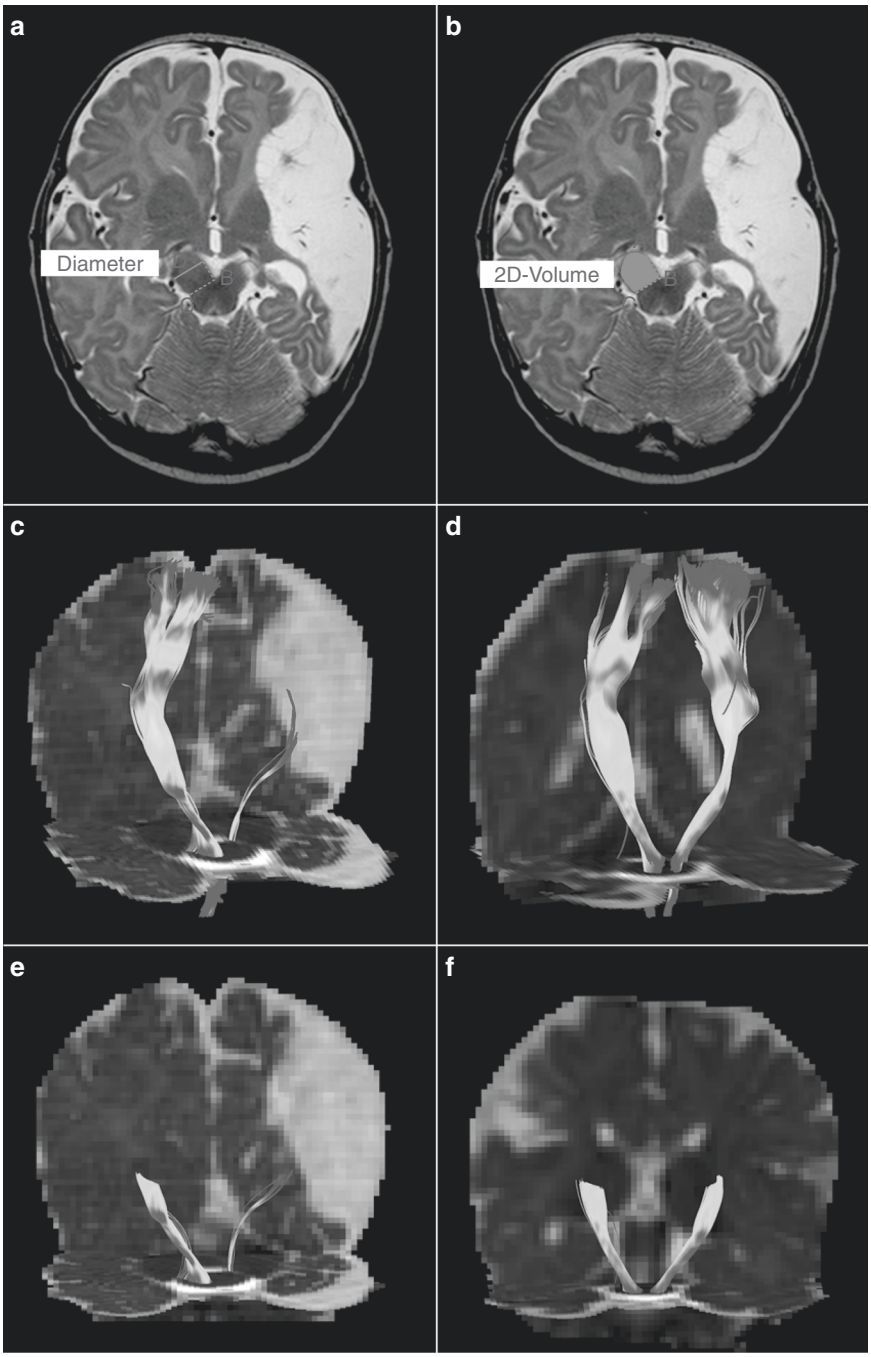

Fig. 1 Example of MRI measurements. Cerebral peduncle measurements were performed on axial T2-weighted images (**a**, **b**). First, a line was drawn parallel to the medio-frontal part of each peduncle, toward the midbrain (**a**, line AB). A second line (**a**, line BC) was drawn perpendicular to this line, crossing the peduncle. The area fronto-lateral to this line was considered to be the 2D surface area of the cerebral peduncle (**b**). Finally, a third line was drawn, parallel to the second at the broadest part of the peduncle, reflecting the width of the peduncle (line D, **a**). Tractography in CSTs of an infant who developed USCP (**c**) and an infant with normal outcome (**d**) using diffusion tensor imaging (DTI). After tractography of the full CST, segments between the PLIC and cerebral peduncle were selected for FA measurements. Clear FA asymmetry is shown in the infant who developed USCP (**e**) compared to a typical developing infant (**f**).

anisotropy (FA) value < 0.1 was entered or if the angle of a fiber between two consecutive steps exceeded 40 degrees.

Following the whole-brain tractography, the CST was identified using two regions of interest (ROIs) as described before.[16] The first ROIs was drawn around the frontal part of the middle cerebral peduncles at the level of crossing pontine fibers where the anterior and posterior parts of the peduncles were completely separated on the color map. The second ROI was drawn around the posterior limb of the internal capsule two to three slices below the corpus callosum. In case tissue loss hindered specific drawing of any of the ROIs based on visible landmarks, a ROI was drawn based on the location and size of the corresponding ROI in the unaffected hemisphere. Fibers passing the two ROIs were identified as the CST. Any fibers continuing into the other hemisphere, the cerebellum, and the medial lemniscus or single aberrant fibers that were considered not to be part of the CST were removed. The segment between the two ROIs was used for further analysis (Fig. 1e, f). The FA was calculated for each CST

segment separately and used to calculate an AI. If no FA could be calculated from the affected CST, this resulted in an AI of 100%. Inter-rater reliability was determined between two researchers by repeating tractography, segment selection, and subsequent FA measurements in 20 CSTs of 10 infants.

Assessment of early motor development

Motor development was assessed using the HAI <5 months, between 5 and 8 and between 8 and 12 months of corrected age. The HAI assessment was performed by a pediatric occupational therapist with expertise in HAI evaluation and who was unaware of the MRI results. The HAI consists of a 15-min play-related session that stimulates unilateral and bilateral upper limb movement.[20] The assessment was video recorded and scored afterwards. The HAI scores 12 items for each individual hand (Contralesional/Ipsilesional each Hand Sum Score, score 0–24 for each hand) and 5 bimanual items creating a total score for both hands combined (Both hand measure, score 0–100) and an AI. For the study, the AI was re-calculated using the each Hand Sum scores for the unaffected and affected hand.

Development of USCP

After discharge from the NICU, children were seen at regular time intervals in the neonatal follow-up clinic. USCP development was assessed at the age of ≥2 years by a pediatric neurologist (L.S.d.V.) who was unaware of the DTI and HAI results using criteria from a report from 2007.[26] Severity of USCP was classified using the Gross Motor Function Classification System (GMFCS).

Statistics

For all conventional MRI, DTI, and HAI measures, an AI was calculated as: AI = ((measure unaffected [MU] − measure affected [MA])/(MU + MA)) × 100%, where affected refers to the affected hemisphere and contralesional hand. IBM SPSS Statistics® v25 (IBM Corp., Armonk, NY) was used for statistical analysis. Patient characteristics were summarized as counts with percentages for categorical variables, means ± standard deviation (SD) for parametric data, and as median ± interquartile ranges for nonparametric data. To test for differences between groups, chi-square test, one-sample *T* tests, paired sample *T* test, independent *T* tests, one-way analysis of variance or the nonparametric variant were used. Receiver operator characteristic (ROC) curves were created using the Prism GraphPad Software (version 7.04 for Windows, GraphPad Software, Inc.) to determine sensitivity and specificity at various AI thresholds. Each threshold value is midway between two values. Optimal cut-off values were determined by calculating the maximal Youden's Index using Youden's *J* = Sensitivity + Specificity − 1. When cut-offs resulted in similar Youden's Index, the cut-off yielding in highest sensitivity was chosen since these predictors are part of a screening test. Area under the curve (AUC) from ROC curves were compared using a calculation as described by Hanley et al.[27]

RESULTS

After admission to the department of Neonatology in the Wilhelmina Children's Hospital in Utrecht, 48 infants with UPBI were considered at risk of developing USCP based on MRI parameters such as involvement of the CST and therefore referred for HAI assessment by the attending physician. Of these, 45 children had HAI data available and were included in this study (Table 1). Of those, 24 were born at term (mean GA 39.5 ± 1.5 weeks) and 21 were born preterm (mean GA 28.7 ± 3.7 weeks). Infants were diagnosed with PVHI ($n = 18$), PAIS ($n = 18$), or other diagnoses, including thalamic hemorrhage ($n = 4$), antenatal PVHI with porencephalic cyst ($n = 3$), parenchymal hemorrhage based on COL4A1 mutation ($n = 1$), and herpes encephalitis with diffuse unilateral lesions ($n = 1$). PHVI was mainly observed in preterm infants ($n = 16$), while PAIS was more common in term born infants ($n = 15$).

After a follow-up of at least 2 years, 27 children (60.0%) were diagnosed with USCP. USCP was diagnosed in 12 term (50%) and 15 (71.4%) preterm born infants. GMFCS could be determined in 23 USCP patients (85%) and was most often grade I (67%).

MR imaging

An MRI scan was acquired in 22 preterm infants (100%) and 20 term born infants (83.3%) at a mean age of 98.5 (±22) and 93.4 (±14.2) days, respectively. This corresponded to a corrected age of 42.9 (±3.7) weeks for preterm and 53.0 (±1.6) weeks for term infants ($p < 0.0001$). A DTI scan of sufficient quality was available in 38 infants (82.6%), as DTI images were not obtained ($n = 2$) or did not reach quality requirements ($n = 2$).

Conventional MRI AIs

Median diameter and volume of the affected (ipsilesional) cerebral peduncle were significantly lower compared to the non-affected cerebral peduncle (Table 2). Also within subgroups of term and preterm infants, most differences between affected and non-affected cerebral peduncle persisted (Table 2). Median AI of peduncle diameter was higher in infants who developed USCP, while peduncle volume measurements did not differ between

Table 2. Measures of MRI, DTI, and HAI in the affected and non-affected side.

	Affected			Non-affected		
	Total	Term	Preterm	Total	Term	Preterm
Peduncle surface in mm^2 ($n = 40$)	76.1 (62.6–98.4)[a]	87.2 (69.3–116.3)[bc]	68.0 (57.0–78.9)[c]	89.6 (66.4–109.8)[a]	106.4 (94.4–117.2)[bc]	69.6 (63.2–84.1)[c]
Peduncle diameter in mm ($n = 40$)	9.6 (8.6–10.5)[a]	9.9 (9.0–10.7)[b]	9.3 (8.5–10.2)[d]	10.3 (9.5–11.3)[a]	10.9 (10.2–11.9)[bc]	9.8 (9.0–10.5)[cd]
FA CST ($n = 37$)	0.31 (0.26–0.40)[a]	0.38 (0.28–0.42)[b]	0.30 (0.22–0.33)[d]	0.41 (0.35–0.44)[a]	0.44 (0.42–0.45)[bc]	0.36 (0.33–0.39)[cd]
HAI < 5 months ($n = 44$)	9.0 (6.0–12.8)[a]	10.0 (5.0–12.8)[b]	9.0 (7.0–15.0)[d]	14.0 (11.0–17.0)[a]	12.0 (11.0–15.8)[bc]	16.5 (12.5–18.5)[cd]
HAI 5–8 months ($n = 32$)	13.5 (6.5–17.8)[a]	14.5 (5.0–20.3)[b]	12.0 (8.8–15.0)[d]	22.0 (21.3–23.0)[a]	22.0 (21.8–23.0)[b]	22.0 (20.8–23.0)[d]
HAI > 8 months ($n = 32$)	16.0 (5.5–21.8)[a]	15.0 (3.0–23.0)[b]	16.0 (12.0–20.0)[d]	24.0 (23.0–24.0)[a]	24.0 (22.3–24.0)[b]	23.5 (23.0–24.0)[d]

Measurements are presented as median (interquartile range)
FA fractional anisotropy, *CST* corticospinal tract, *HAI* hand assessment for infants
[a]Difference between affected/non-affected within total group
[b]Difference between affected/non-affected within term infants
[c]Difference between term and preterm infants
[d]Difference between affected/non-affected within preterm infants

Table 3. Asymmetry indices.

Asymmetry index (%)	Total ($n = 45$)	No USCP ($n = 18$)	USCP ($n = 27$)
Peduncle surface ($n = 40$)	3.0 (−2.9 to 14.4)	1.1 (−3.9 to 7.1)	6.7 (1.1 to 15.0)
Peduncle diameter ($n = 40$)$^{\$}$	3.0 (0.9 to 5.6)	1.4 (−0.1 to 3.4)	3.9 (2.2 to 11.3)
FA CST ($n = 37$)*	8.2 (1.5 to 22.5)	−0.2 (−0.8 to 3.5)	16.6 (8.0 to 34.4)
HAI <5 months ($n = 44$)*	9.7 (0.0 to 42.6)	0.0 (0.0 to 5.9)	38.8 (7.6 to 56.7)
HAI 5–8 months ($n = 32$)*	23.3 (5.4 to 54.1)	2.4 (0.0 to 5.4)	34.3 (21.9 to 65.8)
HAI >8 months ($n = 32$)*	18.0 (2.1 to 53.7)	0.0 (0.0 to 2.1)	31.4 (18.0 to 77.4)

Median (IQR) of asymmetry indices (AI) per predictor for total cohort, and subgroups of infants who developed USCP and those who did not
USCP unilateral spastic cerebral palsy, *FA* fractional anisotropy, *CST* corticospinal tract, *HAI* hand assessment for infants
Differences between subgroups are marked with *$p < 0.0001$ or $^{\$}p < 0.05$

infants with and without USCP (Table 3). There were no differences in cerebral peduncle AI between term and preterm infants ($p > 0.05$). Cerebral peduncle volumes did not significantly differ between researchers in 15 subjects (mean difference −2.1 ± 11.6, $p > 0.1$), and their AI was also similar (mean difference −0.8 ± 5.9, $p > 0.1$). Cerebral peduncle diameter measurements differed between researchers in 15 subjects (mean difference −0.5 ± 0.7 mm, $p < 0.01$), but AI between researchers was similar (mean difference 0.7 ± 3.5 mm, $p > 0.1$).

DTI asymmetry indices

FA values of the CST were not only significantly lower for ipsilesional versus contralesional in the total cohort but also when analyzing term and preterm infants separately (Table 2). FA measurements differed between term and preterm infants in the non-affected CST only. Median AI of FA values were higher in infants who developed USCP compared to those with normal motor development (Table 3). There were no differences in FA AI between term and preterm infants ($p > 0.05$). FA values did not significantly differ between researchers in 20 measurements (mean difference 0.02 ± 0.06, $p > 0.1$), and AI was also similar between researchers in these 10 subjects (mean difference −8.0 ± 27.8, $p > 0.01$).

HAI asymmetry indices

HAI was performed at a corrected age of 14.9 (±2.2), 28.1 (±2.9) and/or 42.1 (±5.1) weeks (Table 1). HAI scores at all timepoints were significantly lower for the affected (contralesional) hand compared to the non-affected (ipsilesional) hand in the total cohort but also when analyzing term and preterm infants separately (Table 2). The ipsilesional each Hand Sum Score <5 months of age differed between term and preterm infants, while other HAI scores did not significantly differ. AI of HAI scores at all timepoints were higher in infants who developed USCP compared to those who did not (Table 3). There were no differences in HAI AIs between term and preterm infants ($p > 0.05$ at all timepoints).

ROC analyses USCP

ROC analyses were performed for all AIs in relation to outcome in the total cohort and for term and preterm infants separately. Optimal cut-off values per AI and their corresponding prediction measures, including sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) are presented in Table 4 and Fig. 2.

Comparing asymmetry indices

To compare the different predictors for USCP, AUC of ROC curves were analyzed. Overall, the AUC of the HAI >8 months of age was highest being 1 and cerebral peduncle measurements yielded lowest AUCs (Table 3). However, as predicting USCP as early as possible is clinically most relevant, we focused on comparing prediction measures at the earliest time period (<5 months of age). At this age, the FA AI on DTI yielded the highest AUC when compared to both conventional MRI indices ($p < 0.05$) and HAI in the first 5 months ($p > 0.05$). When analyzing the preterm infant subgroup, only the FA AI was found to be a significant predictor, where the peduncle surface and diameter and the early HAI were not significant predictors. For term infants, peduncle diameter measurements yielded the highest AUC before 5 months of age, although conventional MRI, DTI, and HAI asymmetry measurements yielded comparable AUC ($p > 0.05$) (Table 4).

DISCUSSION

This study cohort consisted of infants with UPBI who were at high risk of developing motor disabilities in later life. Early risk evaluation is important to adequately counsel families and caregivers and select those infants who might benefit from early intervention strategies to attenuate adverse outcome. These interventions focus on rehabilitation strategies to stimulate activity-dependent plasticity of the developing brain that have proven effective when initiated within the first 3–8 months of life.[9] This study aimed to describe the predictive ability of several quantitative asymmetry measures in order to provide simple cut-offs for the selection of high-risk infants.

UPBI leads to USCP by either primary injury of motor areas or secondary injury of axons of the CST, often referred to as Wallerian degeneration.[12,13] MRI has proven especially useful in evaluating CST involvement, which is highly associated with the development of USCP.[10] However, as visual qualification of CST involvement requires knowledge and experience, quantifying Wallerian degeneration seems preferable.[14] Using a method described by Kirton et al., we indeed found that asymmetry of the descending CST at the level of the cerebral peduncle on conventional MRI corresponded to poor motor outcome.[14,28] However, in our study only diameter, and not volume, of the cerebral peduncle reached significant predictive ability for USCP. This may be explained by the fact that our cohort consisted of preterm infants, in whom Wallerian degeneration is less well described.[29] In addition, we used the complete frontal parts of the cerebral peduncle as a proxy of CST asymmetry, but this structure also consists of other tracts (e.g., frontopontine fibers, corticonucleur fibers, etc) that are not necessarily affected by UPBI.

As findings from us and others suggest, visual inspection of CST asymmetry on conventional MRI is unable to correctly predict USCP in all infants.[21] Kirton et al. therefore suggested the use of "function-specific" imaging with DTI tractography to improve prediction, since it is able to specifically assess motor tracts.[14] As DTI quantifies detailed white matter connectivity, it may also be more sensitive to subtle changes that increase the risk of adverse motor outcome but are not visible on conventional imaging. We confirmed that, before 5 months of age, DTI yielded the highest predictive ability with excellent prediction (AUC 0.94) with 100%

Table 4. Predictive performance of asymmetry indices in the prediction of unilateral spastic cerebral palsy.

Asymmetry index (%)	Total cohort ($n = 45$)	Term ($n = 24$)	Preterm ($n = 21$)
Peduncle surface ($n = 40$)	AUC 0.67* Cut-off 1.7% Sens 71% Spec 63% PPV 74% NPV 59%	AUC 0.79 Cut-off 10.9% Sens 70% Spec 90% PPV 88% NPV 75%	AUC 0.61* Cut-off 1.5% Sens 64% Spec 67% PPV 82% NPV 44%
Peduncle diameter ($n = 40$)	AUC 0.74 Cut-off 1.9% Sens 79% Spec 56% PPV 73% NPV 64%	AUC 0.97 Cut-off 4.7% Sens 90% Spec 100% PPV 100% NPV 91%	AUC 0.51* Cut-off 1.9% Sens 64% Spec 50% PPV 75% NPV 38%
FA CST ($n = 37$)	AUC 0.94 Cut-off 2.6% Sens 100% Spec 73% PPV 85% NPV 100%	AUC 0.92 Cut-off 2.6% Sens 100% Spec 70% PPV 75% NPV 100%	AUC 0.99 Cut-off 6.3% Sens 92% Spec 100% PPV 100% NPV 83%
HAI <5 months ($n = 44$)	AUC 0.85 Cut-off 7.7% Sens 77% Spec 83% PPV 87% NPV 71%	AUC 0.93 Cut-off 2.0% Sens 92% Spec 83% PPV 85% NPV 91%	AUC 0.74* Cut-off 19.9% Sens 64% Spec 100% PPV 100% NPV 55%
HAI 5–8 months ($n = 31$)	AUC 0.99 Cut-off 8.2% Sens 100% Spec 90% PPV 95% NPV 100%	AUC 0.97 Cut-off 6.9% Sens 100% Spec 86% PPV 92% NPV 100%	AUC 1.00 Cut-off 14.2% Sens 100% Spec 100% PPV 100% NPV 100%
HAI >8 months ($n = 32$)	AUC 1.00 Cut-off 5.7% Sens 100% Spec 100% PPV 100% NPV 100%	AUC 1.00 Cut-off 8.0% Sens 100% Spec 100% PPV 100% NPV 100%	AUC 1.00 Cut-off 5.7% Sens 100% Spec 100% PPV 100% NPV 100%

Per index, an area under the curve (AUC) is presented, where asterisk (*) presents non-significant AUC. Optimal cut-offs were calculated using Youden's index and using this cut-off, sensitivity (sens), specificity (spec), positive predictive value (PPV), and negative predictive value (NPV) were calculated
FA fractional anisotropy, *CST* corticospinal tract, *HAI* hand assessment for infants

NPV, which was comparable to our previous studies.[16,17] These are optimal conditions for a screening instrument because it means that, after selecting high-risk infants with DTI, no infants with USCP will be missed for early intervention.

As the follow-up scan is often performed when clinical parameters are also available, we compared both measures for this study. The combination of neuro-imaging and clinical assessment is also recommended as the golden standard for CP prediction.[19] Before 5 months of age, clinical motor assessment is recommended with use of the general movements (GM) and after 5 months of age with the Hammersmith Infants Neurological Examination (HINE).[19,30] However, these tests are not designed for the specific diagnosis of hemiplegia, which is the result of UPBI. Diagnosing hemiplegia focuses on evaluation of movement asymmetry, which is often the first clinical sign of USCP in young infants. Cioni et al. found reduced segmental movements during fidgety movement period (9–16 weeks' postterm) to be more predictive for development of hemiplegia than global abnormalities in GM.[30–32] HAI also aims to assess these segmental distal movements of the upper limbs by scoring the use and quality of both hands separately, however, during goal-directed movements and providing a clinical measure of asymmetry. We found a specificity to predict USCP of HAI asymmetry <5 months of age of 77%, lower than the specificity of HINE and GMs at this age (ranging between 95% and 98%).[19,30] This can potentially be explained because goal-directed intentional movements are still emerging before 5 months age and can therefore be non-asymmetrical due to their bilateral immaturity. A recent study from a Swedish and our group demonstrated that unilateral HAI scores of the affected hand, in combination with GA and gender, had excellent accuracy for USCP prediction before 5 months of age (0.93, 95% confidence interval 0.86–1.00).[33] This also demonstrated that HAI scores may be potentially useful for prediction of USCP, although asymmetry may not be the best HAI measure at an early age. As recently published normative reference values showed that the majority of infants acquire all skills of HAI only after 6 months of age, predictive value of HAI asymmetry may increase after this age.[34] Indeed, our study shows that, after 8 months of age, HAI is able to correctly detect all infants who will develop USCP, comparable to other studies. This demonstrates that HAI may have a potential role to diagnose USCP before the first year of age, although other studies are needed to validate this. A recent study from Hay et al. also described that addition of an asymmetry score to the HINE also helps to distinguish infants with hemiplegia from controls after 5 months of age.[35] The comparison of HAI and these HINE asymmetry scores also needs to be studied further.

This study described differences in predictive ability for MRI asymmetry indices between term and preterm infants. This could be explained by timing of the scan: although postnatal age at the time of MRI did not differ, the postmenstrual age at time of the MRI was approximately 10 weeks shorter for preterm compared to term infants. Consequently, preterm infants had less-developed brains with less myelin, resulting in lower FA values and smaller peduncle measures compared to term infants. Owing to these differences, it may be more difficult to detect asymmetry in preterm infants by conventional imaging, while DTI is more sensitive to minor asymmetry changes in white matter connectivity.

We also found differences between term and preterm infants in the predictive ability of HAI. Hand function asymmetry was highly predictive before 5 months of corrected age in term infants, while it was not in preterm infants. This could potentially be a result of differences in lesion type, which is closely linked to prematurity. PVHI was the most prevalent type of UPBI in preterm infants, while it was PAIS for term infants. It has been described that periventricular lesions, such as PVHI, usually result in milder USCP than lesions in the cortex, subcortical area, and basal ganglia, as seen in PAIS.[36] In addition, hand function after early brain injury is influenced by reorganization of the CST, which is affected by both lesion type and age of onset of the lesion.[37] Future studies are necessary to investigate the distinctive effects of UPBI type and premature birth on asymmetric hand function.

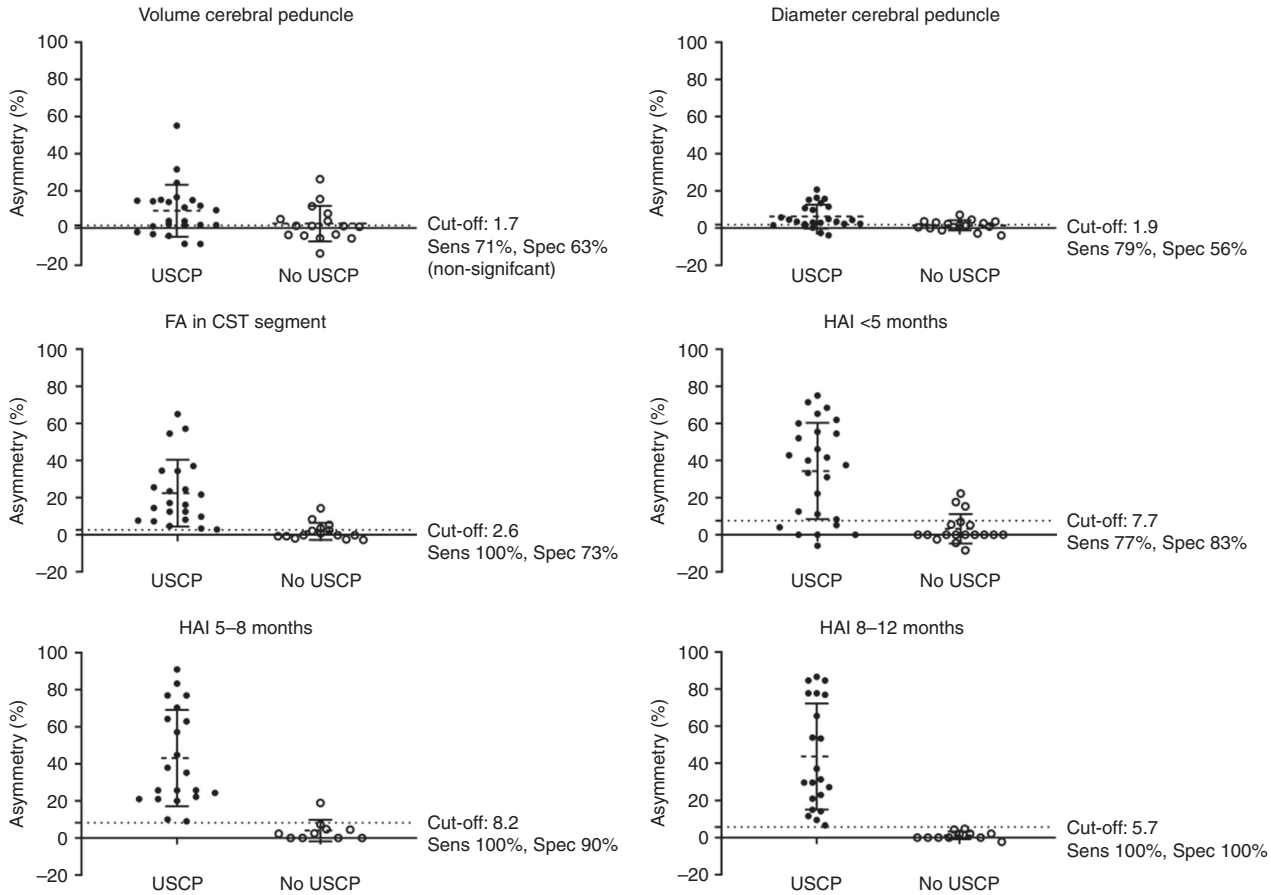

Fig. 2 Graphic representation of asymmetry indices for total cohort. Per asymmetry index, optimal cut-offs to predict unilateral spastic cerebral palsy were calculated using Youden's index and sensitivity (sens) and specificity (spec) were calculated. FA fractional anisotropy, CST corticospinal tract, HAI hand assessment for infants, USCP unilateral spastic cerebral palsy.

There are some limitations to this study. The HAI is a relatively new instrument that requires a trained assessor to perform the assessment (10 min testing+30 min assessment) during clinical follow-up. Therefore, only infants at high risk of developing USCP based on MRI findings were followed up by HAI in our hospital and eligible for this study. The results of this study should therefore be validated in a population at lower risk before extrapolation to the general population. Second, extensive MRI post-processing techniques such as DTI tractography assumes strict scanning protocols without movement artifacts, leading to exclusion of several cases. Furthermore, this study focused on the use of follow-up MRI instead of early MRI within days after birth, limiting its role for selecting candidates for early neuroprotective therapies. Previous studies have shown that asymmetry in FA of the CST is already predictive of motor outcome after UPBI when DTI is obtained within 4 weeks after birth.[16,21,28] However, as DTI is prone to movement artifacts, it is more difficult to perform in preterm infants before term-equivalent age.[38,39] In addition, DTI is especially sensitive to injury, and tractography is often unreliable in the presence of acute edema/injury. Furthermore, secondary injury to the descending CST takes time to develop.[40] This resulted in the use of follow-up MRI including DTI for this study, while conventional MRI tools may potentially be more useful when obtained earlier in life.

CONCLUSION

Prediction of USCP in children with UPBI can be done by asymmetry of the CST on conventional MRI and DTI, as well as clinical hand assessment. This study revealed that, before 5 months of age, DTI tractography provides strongest predictive information in both preterm and term born infants. Asymmetry as measured by HAI does not seem to be the best clinical tool for early prediction as other assessments that focus on spontaneous movements (GMs, HINE) have higher predictive values in the literature, while we found that HAI asymmetry specifically aids to prognosis of USCP at later age points. Therefore, HAI might be of additional value in the infants in whom follow-up MRI and/or DTI is not performed or its result is uncertain. Combining several quantitative asymmetry indices could potentially select all infants with UPBI who are at high risk for developing USCP who could benefit from intervention strategies.

ACKNOWLEDGEMENTS

We thank Robin van Aggele for his help with cerebral peduncle measurements. N.W. was supported by the Netherlands Organisation for Health Research and Development (ZonMW), the Netherlands (TAS Research Grant 11600200). C.H.V. was supported by the Phelps Foundation. The research of A.L. is supported by VIDI Grant 639.072.411 from the Netherlands Organisation for Scientific Research (NWO). This study received no specific financial support.

AUTHOR CONTRIBUTIONS

All individuals listed as authors met the appropriate authorship criteria. N.W. wrote the first draft of the manuscript. N.E.v.d.A. has contributed to the conception and design of the manuscript. C.H.V., C.K. and B.P.L.v.G. contributed to collection and analysis of the data. N.W., L.S.d.V., F.G., A.L., M.J.N.L.B. and N.E.v.d.A. have made substantial contributions to the acquisition and interpretation of data for the work.

All authors contributed to drafting the manuscript or revised it critically with respect to its intellectual content; and each author has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. Nobody who qualifies for authorship has been omitted from the list.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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