Corticospinal Tract Injury Precedes Thalamic Volume Reduction in Preterm Infants with Cystic Periventricular Leukomalacia

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Objectives To measure both fractional anisotropy (FA) values in the corticospinal tracts (CSTs) and volume of the thalami in preterm infants with cystic periventricular leukomalacia (c-PVL) and to compare these measurements with control infants.

Study design Preterm infants with c-PVL and controls with magnetic resonance imaging data acquired between birth and term equivalent age (TEA) were retrospectively identified in 2 centers. Tractography of the CST and segmentation of the thalamus were performed, and values from infants with c-PVL and controls were compared.

Results Thirty-three subjects with c-PVL and 31 preterm controls were identified. All had at least 1 scan up to TEA, and multiple scans were performed in 31 infants. A significant difference in FA values of the CST was found between cases and controls on the scans both before and at TEA. Absolute thalamic volumes were significantly reduced at TEA but not on the earlier scans. Data acquired in infancy showed lower FA values in infants with c-PVL.

Conclusions Damage to the CST can be identified on the early scan and persists, whereas the changes in thalamic volume develop in the weeks between the early and term equivalent magnetic resonance imaging. This may reflect the difference between acute and remote effects of the extensive injury to the white matter caused by c-PVL. *(J Pediatr 2015;167:260-8)*.

Despite the decreasing incidence, cystic periventricular leukomalacia (c-PVL) remains one of the leading causes of cerebral palsy (CP) after preterm birth.[1,2] Around 1%-3% of preterm infants will have c-PVL,[1-3] and in over 60% of them, this will develop CP.[2,4] Early recognition of infants at risk of CP is important, both for accurate counseling of parents as well as for a possible selection of infants that may benefit from early behavioral interventions or rehabilitation services.[5] Assessment of the myelination of the posterior limb of the internal capsule (PLIC) on conventional magnetic resonance imaging (MRI) at term equivalent age (TEA) can reliably predict the development of CP in most infants.[6] However, the severity of CP as well as cognitive and behavioral outcomes and the development of epilepsy, remain difficult to predict.

Over the last decade, the use of diffusion tensor imaging (DTI) has made the in vivo assessment of early human brain development possible on a microstructural level, providing a better understanding of both the direct and remote effects of injury to white or gray matter.[7]

Several studies have shown a correlation between the presence and severity of CP after periventricular leukomalacia (PVL) and fractional anisotropy (FA) in the corticospinal tract (CST) as a measure of white matter injury in childhood. FA measurements were lower in children with CP compared with healthy controls, and also lower in children who were more severely impaired compared with those with mild, ambulatory CP.[8-10] It is, however, unclear when these differences develop because these studies were performed in older children. Studies in the neonatal period are few, and often include infants with non-c-PVL, which may influence the results.[11] This is also the case for neonatal studies assessing thalamic involvement in children with CP after PVL. Thalamic involvement is thought to occur as a secondary process to white matter injury, and

AD	Axial diffusivity	NPV	Negative predictive value
AUC	Area under the curve	PLIC	Posterior limb of the internal capsule
CP	Cerebral palsy		
c-PVL	Cystic periventricular leukomalacia	PMA	Postmenstrual age
CST	Corticospinal tract	PPV	Positive predictive value
DTI	Diffusion tensor imaging	PVL	Periventricular leukomalacia
FA	Fractional anisotropy	RD	Radial diffusivity
GA	Gestational age	TBV	Total brain volume
GMFCS	Gross motor function classification system	TE	Echo time
		TEA	Term equivalent age
MD	Mean diffusivity	TR	Repetition time
MRI	Magnetic resonance imaging		

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thalamic volumes were reduced in children with CP compared with healthy controls.[12,13] Again, this appears to be related to the severity of CP in childhood,[14,15] but it is unclear when these differences develop.

The aim of our study was to test the hypothesis that FA values in the CST and thalamic volumes in preterm infants with c-PVL, scanned during the early neonatal period and again around TEA, are lower compared with these measurements in control infants. In addition, we aimed to assess the association between these measures and gross motor outcome in infancy.

Methods

For this study, all infants born below a gestational age (GA) of 36 weeks with a clinical diagnosis of c-PVL on cranial ultrasound and at least 1 MRI during the neonatal period were retrospectively identified. Infants born between March 2005 and September 2013 from both the Wilhelmina Children's Hospital in Utrecht, The Netherlands and Queen Charlotte's and Chelsea Hospital in London, United Kingdom, were eligible for inclusion. Permission for MRI was granted by the Research Ethics Committees at both institutions. PVL grading was determined on sequential cranial ultrasound, according to de Vries et al.[16] Scans were obtained within the first few weeks after the insult occurred as assessed from cranial ultrasound scans in most patients and were repeated at TEA. Preterm control infants without significant brain injury on their MRI and normal motor development at follow-up around 15 months corrected age were randomly selected from our preterm population and were matched for sex. Scans in the controls were done around 30 weeks postmenstrual age (PMA) for infants with a GA <28 weeks and soon after birth on clinical indication in those with a GA >28 weeks, and were repeated at TEA. For a subgroup of patients with c-PVL, scans in infancy were also available (n = 10, 5 from Utrecht, 4 from London, with 1 of the infants from London scanned twice). Three control infants from London were scanned in infancy, and no control scans during infancy from Utrecht were available. Outcome data were collected from the patient charts. Neurodevelopmental outcome was formally assessed in the out-patient follow-up clinic, and all children had a standard clinical neurologic examination. Severity of CP was graded according to the gross motor function classification system (GMFCS).[17]

MRI

For the infants from Utrecht, MRI was performed on either a 1.5 Tesla ACS-NT system or a 3 Tesla whole-body Achieva system (Philips Medical Systems, Best, The Netherlands) with the phased array head coil. On the 1.5T magnet, the routine protocol included conventional inversion recovery-weighted imaging and T2-weighted imaging (30 and 40 weeks: inversion recovery-weighted repetition time [TR] 4147 ms; inversion time 600 ms; echo time [TE] 30 ms; slice thickness 2 mm and T2-weighted TR 7656 ms; TE 150 ms; slice thickness 2 mm) and on the 3T magnet, the routine protocol included conventional 3-dimensional T1-weighted and T2-weighted imaging (30 weeks: 3-dimensional T1-weighted TR 9.4 ms; TE 4.6 ms; slice thickness 2 mm and T2-weighted TR 10 085 ms; TE 120 ms; slice thickness 2 mm; 40 weeks: 3D T1-weighted TR 9.5 ms; TE 4.6 ms; slice thickness 1.2-2 mm and T2-weighted TR 4847-6293 ms; TE 120-150 ms; slice thickness 1.2-2 mm). The DTI protocol consisted of a single-shot spin-echo echo-planar imaging sequence (echo-planar imaging factor 55, TR 5685 ms, TE 70 ms, field of view 180 × 146 mm, acquisition matrix 128 × 102 mm (voxel size 1.41 × 1.43 × 2.0 mm), 2 mm slice thickness without gap, SENSE factor 2). Images were acquired in the axial plane with diffusion gradients applied in 32 noncollinear directions with a b-value of 800 s/mm^2 and 1 nondiffusion-weighted image. In infancy, all children were scanned on a 1.5T magnet. A similar single-shot echo-planar imaging sequence was used but with an echo-planar imaging factor of 51, TR of 8382 ms, and field of view of 192 × 192 mm. Infants from London were scanned on a Philips 3 Tesla system (Philips Medical Systems, Best, The Netherlands) using an 8-channel phased array head coil. T2-weighted fast-spin echo MRI was acquired using TR 8670 ms; TE 160 ms; slice thickness 2 mm with 1 mm overlapping slices and T1-weighted imaging using TR 17 ms, TE 4.6 ms, slice thickness 0.8 mm. Single shot echo-planar imaging DTI was acquired in the transverse plane in 32 noncollinear directions using the following variables: echo planar imaging factor 59, TR 8000 ms, TE 49 ms, field of view 224 mm, acquisition matrix 128 × 128 (voxel size 1.75 × 1.75 × 2.0 mm), 2 mm slice thickness, b-value 750 s/mm^2, SENSE factor of 2.

Infants in Utrecht were sedated for the first 2 scans, using oral chloral hydrate 50-60 mg/kg, and in London only for the TEA scan (30-55 mg/kg), according to the local clinical protocol. A neonatologist was present throughout all examinations. In infancy, children in Utrecht received general anesthesia and were monitored by an anesthetist, and those in London were sedated with oral chloral hydrate (50-80 mg/kg) and monitored by an experienced pediatrician.

For all MRIs obtained around TEA, the presence and quality of myelination in the PLIC were scored retrospectively (F.C., L.d.V) as either normal or abnormal/absent, using both T1- and T2-weighted sequences. Scoring was performed blinded to outcome data.

Postprocessing of Volumetric Data

T2-weighted scans during the neonatal period were segmented using the neonatal specific segmentation method of Makropoulos et al.[18] This method utilizes an expectation-maximization scheme that combines manually labeled atlases[19] with intensity information from the image to be segmented and has shown reliable results among infants scanned at PMA ranging between 28 and 44 weeks.[18,20] All segmentations were manually checked, and small corrections were performed if necessary. An example of segmentation results in cases and controls is presented in **Figure 1** (available at www.jpeds.com).