Diffusion Tractography Biomarkers of Pediatric Cerebellar Hypoplasia/Atrophy: Preliminary Results Using Constrained Spherical Deconvolution

S. Fiori, A. Poretti, K. Pannek, R. Del Punta, R. Pasquariello, M. Tosetti, A. Guzzetta, S. Rose, G. Cioni, and R. Battini

ABSTRACT

BACKGROUND AND PURPOSE: Advances in MR imaging modeling have improved the feasibility of reconstructing crossing fibers, with increasing benefits in delineating angulated tracts such as cerebellar tracts by using tractography. We hypothesized that constrained spherical deconvolution–based probabilistic tractography could successfully reconstruct cerebellar tracts in children with cerebellar hypoplasia/atrophy and that diffusion scalars of the reconstructed tracts could differentiate pontocerebellar hypoplasia, nonprogressive cerebellar hypoplasia, and progressive cerebellar atrophy.

MATERIALS AND METHODS: Fifteen children with cerebellar ataxia and pontocerebellar hypoplasia, nonprogressive cerebellar hypoplasia or progressive cerebellar atrophy and 7 controls were included in this study. Cerebellar and corticospinal tracts were reconstructed by using constrained spherical deconvolution. Scalar measures (fractional anisotropy and mean, axial and radial diffusivity) were calculated. A general linear model was used to determine differences among groups for diffusion MR imaging scalar measures, and post hoc pair-wise comparisons were performed.

RESULTS: Cerebellar and corticospinal tracts were successfully reconstructed in all subjects. Significant differences in diffusion MR imaging scalars were found among groups, with fractional anisotropy explaining the highest variability. All groups with cerebellar pathologies showed lower fractional anisotropy compared with controls, with the exception of cerebellar hypoplasia.

CONCLUSIONS: This study shows the feasibility of constrained spherical deconvolution to reconstruct cerebellar and corticospinal tracts in children with morphologic cerebellar pathologies. In addition, the preliminary results show the potential utility of quantitative analysis of scalars of the cerebellar white matter tracts in children with cerebellar pathologies such as cerebellar hypoplasia and atrophy. Further studies with larger cohorts of patients are needed to validate the clinical significance of our preliminary results.

ABBREVIATIONS: AD = axial diffusivity; CA = progressive cerebellar atrophy; CH = nonprogressive cerebellar hypoplasia; CPCT = corticopontocerebellar tract; CST = corticospinal tract; CTT = cerebellar-thalamic tract; dMRI = diffusion MR imaging; FA = fractional anisotropy; MD = mean diffusivity; PCH = pontocerebellar hypoplasia; RD = radial diffusivity

Received July 24, 2015; accepted after revision September 29.

From Istituto di Ricovero e Cura a CarattereScientifico Stella Maris Foundation (S.F., R.D.P., R.P., M.T., A.G., G.C., R.B.), Pisa, Italy; Section of Pediatric Neuroradiology (A.P.), Division of Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins School of Medicine, Baltimore, Maryland; Commonwealth Scientific and Industrial Research Organization (K.P., S.R.), Centre for Computational Informatics, Brisbane, Australia; Department of Computing (K.P.), Imperial College London, London, United Kingdom; and Department of Clinical and Experimental Medicine (A.G., G.C.), University of Pisa, Pisa, Italy.

In past years, there has been an increasing interest in the application of advanced MR imaging techniques for in vivo investigation of WM microstructure by using diffusion MR imaging (dMRI).1 dMRI provides image contrast based on differences in the magnitude of diffusion of water molecules in the brain.2 By combining the directional information and magnitude of anisotropic diffusion of the individual voxels, the trajectories of the main WM tracts in the brain can be reconstructed2,3 and quantitative analysis of WM organization can be performed.2 dMRI scalars can be measured in specific anatomic ROIs or within/along reconstructed WM tracts to measure tissue properties.2 Several studies have shown that advanced fiber tractography algorithms provide invaluable qualitative and quantitative information on the brain WM microstructure that cannot be obtained with conventional structural neuroimaging sequences.2,4

Developments in high-angular-resolution diffusion imaging5,6 and progress in postprocessing software that take into ac-
count multiple fiber orientations in the same voxel have improved the correct anatomic reconstruction of WM tracts such as the afferent and efferent cerebellar pathways by accommodating crossing fibers. Improvements in fiber tractography of the cerebellar pathways are important because a large number of congenital, acquired, or degenerative diseases of pediatric and adult populations affect the cerebellum.

Currently, the diagnosis of nonprogressive cerebellar hypoplasia (CH) and progressive cerebellar atrophy (CA) is based on qualitative criteria that take into account conventional, structural MR imaging sequences. CH refers to a developmental (non-progressive) reduction of cerebellar volume with preserved normal shape, while CA is defined as progressive loss of cerebellar parenchyma, with secondary enlargement of the interfolium space. In some diseases with prenatal onset, hypoplasia of the cerebellum may be associated with pontine hypoplasia (ie, ponsocerebellar hypoplasia [PCH]). Despite improvement of structural MR imaging techniques (eg, phased array and higher magnetic field), differentiation of CH and CA remains challenging, particularly when only 1 MR imaging study is available. A correct distinction between CH and CA is important in terms of management, prognosis, and family counseling. Neuroimaging methods that may increase the sensitivity in the diagnosis of CH and CA are warranted.

We aimed to study the feasibility of constraint spherical deconvolution fiber tractography to reconstruct cerebellar WM tracts and corticospinal tracts (CSTs) in children with PCH, CH, and CA. We hypothesized that despite different degrees of reduction of cerebellar volumes, our approach could successfully reconstruct cerebellar tracts. In addition, we aimed to measure microstructural properties of cerebellar tracts and CSTs in patients and age-matched controls. We expected that the reconstructed WM tracts would show altered scalar metrics in patients compared with controls. Differences in dMRI scalars of the cerebellar tracts and CSTs among the 3 groups of patients may shed light on the underlying pathomechanism causing macroscopic cerebellar abnormalities and may facilitate the differentiation among the 3 groups of diseases.

**MATERIALS AND METHODS**

**Subjects**

Children with cerebellar ataxia for this prospective study were recruited at Stella Maria Scientific Institute from June 2013 to January 2015 and underwent MR imaging as part of their clinical diagnostic work-up. Inclusion criteria for this study were evidence of isolated PCH, CH, or CA on structural conventional MR imaging and the availability of 2 structural MR imaging studies at least 1 year apart to clearly differentiate CH and CA. On the basis of the 2 structural neuroimaging studies, all patients were classified into the following groups: CH, PCH, and CA. Children with supratentorial abnormalities were excluded from the study. Age-matched typically developing children were recruited as controls. The institutional review board approved the study, and informed parental consent was obtained for all participants.

**Data Acquisition**

MR imaging data were acquired by using a 1.5T MR imaging scanner (Signa Horizon 1.5; GE Healthcare, Milwaukee, Wisconsin). A high-resolution structural 3D T1 BRAVO sequence (GE Healthcare) was acquired by using the following parameters: section thickness, 0.9 mm; FOV, 25.6 × 31.5 cm; TR/TE, 12.36/5.18 ms; flip angle, 13°. The acquisition time was 4 minutes and 30 seconds. dMRI data were acquired by using an echo-planar multidirection diffusion-weighted sequence. The imaging parameters were the following: 45 axial sections; section thickness, 3 mm; FOV, 24 × 29.6 cm; acquisition matrix, 80 × 80 (in-plane resolution, 3.0 × 3.7 mm²); TR/TE, 11,000/92 ms. dMRI data were acquired along 30 noncollinear directions by using a b-value of 1000 s/mm², in which the encoding gradients were distributed in space by using the electrostatic approach. In addition, 1 measurement without diffusion weighting (b=0 s/mm²) was performed. The dMRI acquisition time was 6 minutes.

**Structural Image Analysis**

Structural images were assessed by an experienced pediatric neuroradiologist (R.P.). All MR imaging studies were qualitatively evaluated for the presence of CH, PCH, or CA according to published diagnostic criteria. Supratentorial structures were systematically assessed to exclude children with cerebral involvement.

**dMRI Data Analysis and Fiber Tractography**

An extensive preprocessing procedure was performed to detect and correct image artifacts caused by involuntary head motion, cardiac pulsation, and intensity inhomogeneities, as previously described, by using FSL tools (http://www.fmrib.ox.ac.uk/fsl), ANTS (http://picsl.upenn.edu/software/ants/), and in-house tools. Constrained spherical deconvolution was used to estimate the fiber-orientation distribution for fiber tractography with the MRtrix package (http://neuro.debian.net pkgs/mrtrix.html). To facilitate manual ROI placement, we generated a short-track color-encoded track-density image by using 5 million streamlines of a maximum length of 2 cm seeded throughout the entire brain volume. Cerebellar tracts were reconstructed on the basis of a multi-ROI approach (On-line Figure).

The corticopontocerebellar tract (CPCT) constitutes the main afferent pathway from the cerebral cortex to the cerebellum. To identify the CPCT, we placed a seeding ROI in the middle cerebellar peduncle (drawn on the coronal plane of the track-density image map in the green area [anteroposterior fiber direction]) and an inclusion ROI in the posterior limb of the internal capsule (drawn on the axial plane of the color-coded track-density image in the blue area [top-down fibers direction]). Frontal, parietal, and occipital projections to the cerebellum were included. ROIs were drawn separately for the right and left sides.

The cerebellar-thalamic tract (CTT) is the main efferent tract from the cerebellum. To identify the CTT, we placed a seeding ROI in the superior cerebellar peduncle (drawn on the coronal plane of the track-density image map in the light blue area [anteroposterior mixed with top-down fiber direction, more vertically displaced compared with CPCT]) separately on the right and left sides.
The CST originates from the precentral areas and descends through the centrum semiovale and ipsilateral posterior limb of internal capsule. To identify the CST, we chose the posterior limb of the internal capsule as the seeding ROI. An additional ROI was placed in the cerebral peduncle, on the right and left sides separately, on the axial plane of the color-coded track-density image, according to WM atlas mapping.

Ten thousand streamlines were generated from the seeding ROIs. The maximum number of attempts (ie, number of seeded streamlines) was 1 million. Several exclusion ROIs were systematically placed to remove aberrant fibers.

Tracts were visually examined by 2 experienced raters (R.P. and S.F.) on all subjects to verify trajectory and anatomic landmarks described in the referenced atlas of human WM and to check false-positive streamlines.

Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated as weighted mean values within each tract.

**Statistical Analysis**
For all subjects, several dMRI scalars were calculated for each reconstructed tract. For each tract, a t test was used to compare dMRI scalars of the right and left sides. When no significant differences were found, the mean values of the right and left sides were averaged for further analysis.

A general linear model incorporating age as a covariate of no interest was used to determine the difference among groups for fiber tractography scalar measures (FA, MD, AD, RD). Post hoc pair-wise comparisons were performed to correct for multiple comparisons (Bonferroni-corrected P values).

Statistical analysis was performed by using SPSS, Version 2.0 (IBM, Armonk, New York), and all P values were 2-tailed. Results were considered significant at P < .05.

**RESULTS**

**Subjects**
Fifteen children (mean age, 8.8 ± 4.9 years; range, 4–16 years) with cerebellar abnormalities and 7 normally developing controls (mean age, 9.8 ± 4.2 years; range, 4–16 years) were recruited for this study. On the basis of structural MR imaging studies, patients were classified as follows: 5 children had CH (mean age, 14.2 ± 2.3 years; range, 11–17 years), 5 patients had PCH (mean age, 6.2 ± 4.3 years; range, 3–11 years), and 5 had CA (mean age, 6.2 ± 3.1 years; range, 3–9 years). Detailed demographic, clinical, and genetic information of the 15 patients are shown in On-line Table 1.

Tracts were successfully reconstructed in all subjects (Fig 1); however, fewer than 10,000 streamlines were generated in all groups for both the CPCT (mean number, 8050.89 ± 2076.61) and the CTT (mean number, 5236.67 ± 1731.02), with no differences across groups or controls. No significant differences emerged in scalar measures between the right and left sides. Averaged means and SD of dMRI scalars for each tract are reported in Table 1. Results for FA and MD are plotted in Fig 2. All pair-wise comparisons for averaged scalar measures of each tract are reported in Table 2.

**Corticopontocerebellar Tract**
There were significant differences among the groups in FA (P < .001, R² = 0.89), MD (P = .005, R² = 0.59), and RD (P = .001, R² = 0.71). Post hoc analysis revealed that compared with controls, FA was reduced in PCH (Bonferroni-corrected P value < .001) and CA (Bonferroni-corrected P value = .002). PCH showed lower FA compared with CH (Bonferroni-corrected P values < .001) and CA (Bonferroni-corrected P values = .001). In addition, in PCH MD (Bonferroni-corrected P values = .005) and RD (Bonferroni-corrected P values < .001) values were higher compared with those of controls. No differences were found between controls and CH.

**Cerebellar-Thalamic Tract**
There were significant differences between groups in FA (P < .001, R² = 0.80) and RD (P = .014, R² = 0.49). Post hoc analysis revealed that compared with controls, FA was significantly lower in PCH (Bonferroni-corrected P value < .001) and CA (Bonferroni-corrected P value < .001). PCH (Bonferroni-corrected P value = .001) and CA (Bonferroni-corrected P value = .019) showed lower FA compared with CH. Furthermore, PCH (Bonferroni-corrected P value = .041) and CA (Bonferroni-corrected P value = .028) showed higher RD compared with controls. No differences were detected between controls and CH.

**Corticospinal Tract**
There were significant differences among groups in FA (P < .001, R² = 0.89), AD (P = .003, R² = 0.56), and RD (P < .001, R² = 0.75). Post hoc analysis revealed that compared with controls, FA was lower in PCH (Bonferroni-corrected P value < .001) and CA (Bonferroni-corrected P value < .001). PCH showed lower FA compared with CH (Bonferroni-corrected P value < .001) and CA (Bonferroni-corrected P value = .041). Furthermore, PCH showed higher MD compared with controls (Bonferroni-corrected P value = .005) and higher RD compared with both controls (Bonferroni-corrected P value < .001) and CA (Bonferroni-corrected P value = .045). Finally, CA showed lower AD (Bonferroni-corrected P value = .043) compared with controls. No differences were detected between controls and CH.

**DISCUSSION**
This study shows a 100% success rate for fiber tractography reconstruction of afferent (CPCT) and efferent (CTT) cerebellar tracts and the CST in children with CH, PCH, and CA. We used probabilistic tractography with constrained spherical deconvolution to reconstruct the WM tracts. In adults with ataxic syndromes, previous studies showed that probabilistic tractography is more accurate and less variable compared with deterministic tractography in reconstructing WM tracts within the cerebellar peduncles. However, our very high successful rate is not straightforward because traditional tensor techniques have serious limitations in regions of crossing fibers due to the inability to represent multiple, independent intravoxel orientations. The superior cerebellar peduncles are the main component of the CTT and cross the midline in the midbrain at the level of the inferior colliculus. The dorsomedial portion of the superior cerebellar peduncle and its ventral fibers are the first to decussate, while the middle part de-
cussates at a more rostral level. The middle cerebellar peduncle represents the last portion of the CPCT. Middle cerebellar peduncles connect the brain stem nuclei with the contralateral cerebellar hemisphere and cross the midline at the level of the pons. Constrained spherical deconvolution is a new and innovative model of the diffusion signal that allows the resolution of crossing fibers in voxels containing multiple fiber orientations. Compared with classic tensor models, it improves the estimated fiber orientations present in each voxel, which is especially important for fiber tractography of bundles with abundant crossing fibers, such as the cerebellar tracts, and allows a more accurate reconstruction of WM tracts.

High-order probabilistic fiber tractography models provide not only qualitative but also quantitative information, and dMRI scalars (FA, MD, AD, and RD) can be measured. The results of our study show differences in dMRI scalars of the cerebellar tracts and CST among the 3 groups of patients and controls. Our findings further support the high value of quantitative analysis of dMRI scalars to assess tissue microstructural properties in children with different cerebellar diseases. dMRI scalars are derived from tensor eigenvalues and depend on WM characteristics such as axonal density and the size and degree of myelination. AD describes water molecule mobility along the main fiber orientation axis (estimates axonal injury), while RD describes water mobility perpendicular to the fiber axis (estimates myelin injury). FA describes the relationship between AD and RD and is related to MD (eg, often a decrease in FA is associated with an increase in MD and RD). Each dMRI scalar, however, can be affected by different tissue properties. In our study, FA values explained the highest amount of variability across groups, in agreement with previous studies. MD changed consistently with FA as shown in Fig 2 but explained across-group variability to a lesser degree.

Post hoc analysis revealed differences in FA and RD values between children with cerebellar pathologies and controls, with the exception of patients with CH. Compared with controls, changes in MD reached statistical significance only in the

| Table 1: Mean and SD of FA, MD, AD, and RD within the CPCT, CTT, and CST |
|---------------------------------------------------------------|
| Tract/Group | FA Mean (SD) | MD Mean (SD) (10⁻³ mm²/s) | AD Mean (SD) (10⁻³ mm²/s) | RD Mean (SD) (10⁻³ mm²/s) |
|----------------|-------------|----------------------|----------------------|----------------------|
| CPCT          |             |                      |                      |                      |
| CH            | 0.42 (0.03) | 0.98 (0.11)          | 1.42 (0.12)          | 0.76 (0.09)          |
| PCH           | 0.27 (0.04) | 1.34 (0.14)          | 1.41 (0.08)          | 0.99 (0.14)          |
| CA            | 0.35 (0.03) | 0.99 (0.03)          | 1.36 (0.03)          | 0.81 (0.04)          |
| Control       | 0.44 (0.02) | 0.88 (0.07)          | 1.37 (0.09)          | 0.66 (0.06)          |
| CTT           |             |                      |                      |                      |
| CH            | 0.28 (0.03) | 1.39 (0.11)          | 1.79 (0.09)          | 1.26 (0.17)          |
| PCH           | 0.19 (0.03) | 1.49 (0.18)          | 1.79 (0.23)          | 1.39 (0.14)          |
| CA            | 0.22 (0.02) | 1.59 (0.14)          | 1.68 (0.21)          | 1.41 (0.15)          |
| Control       | 0.29 (0.02) | 1.29 (0.17)          | 1.81 (0.19)          | 1.27 (0.21)          |
| CST           |             |                      |                      |                      |
| CH            | 0.44 (0.02) | 1.07 (0.29)          | 1.69 (0.16)          | 0.91 (0.11)          |
| PCH           | 0.31 (0.03) | 1.29 (0.13)          | 1.71 (0.19)          | 1.08 (0.11)          |
| CA            | 0.36 (0.03) | 1.06 (0.06)          | 1.46 (0.05)          | 0.86 (0.06)          |
| Control       | 0.45 (0.02) | 0.97 (0.04)          | 1.43 (0.06)          | 0.73 (0.04)          |
Further studies including a larger and more homogeneous group of patients with PCH may elucidate the detailed pathomechanism leading to dMRI changes in GM or WM tracts within and outside of the cerebellum.

In children with CA, we found reduced FA compared with controls and CH in all reconstructed WM tracts and an increase in RD in the CTT, including the superior cerebellar peduncle. In addition, subjects with PCH showed higher MD and RD compared with controls in the CPCT and CST and higher RD in the CTT compared with controls. These findings support an involvement of WM tracts outside the cerebellum as previously shown by neuropathology studies. In addition, neuropathology studies in PCH showed regressive (primary) changes with cystic formation in the cerebellar WM. Degenerative cystic formation in the cerebellar WM causes an increase in isotropically diffusing water and, hence, a marked increase in MD as we found in the CPCT (including the middle cerebellar peduncle) of children with PCH. This explanation applies at least to 2 of the 5 patients with PCH. Three subjects with PCH had mutations in the CASK gene. CASK-related PCH is rather of a malformative, not degenerative, nature. Neuropathology findings in a 2-week-old male patient revealed mainly GM involvement. A more recent study, however, showed a role of CASK in axonal outgrowth and branching, supporting WM involvement as shown by our results. Further studies including a larger and more homogeneous group of patients with PCH may elucidate the detailed pathomechanism leading to dMRI changes in GM or WM tracts within and outside of the cerebellum.

In children with CA, we found reduced FA compared with controls and CH in all reconstructed WM tracts and an increase in RD in the CTT, including the superior cerebellar peduncle. In neuronal ceroid lipofuscinosis and congenital disorders of glycosylation type 1a due to PMM2 mutation, neuropathology studies showed that the primary involvement affected the cerebellar cortex with extensive loss of Purkinje cells and granule cells. Neuropathology studies and our findings (decrease in FA and increase in RD without significant changes in MD) suggest that involvement of the cerebellar WM is most likely of a secondary nature.
Atrophy of the cerebral cortex and abnormalities of the cerebral cortex. However, we believe that this does not only within the cerebellar tracts but also in the CST. This finding may reflect a more diffuse involvement as shown in PCH. In neuronal ceroid lipofuscinosis, atrophy of the cerebral cortex and periventricular WM abnormalities have been reported. Atrophy of the cerebral cortex and abnormalities of the subcortical WM have also been shown in congenital disorders of glycosylation type I. Although no supratentorial abnormalities were detected in our patients on conventional MR imaging, changes in the CST may be secondary to ongoing injury of the cerebral cortex and subcortical WM.

In children with CH, we did not find differences in scalars compared with controls. This result is in contrast with the findings in CA and PCH. The lack of differences in dMRI scalars between children with CH and controls suggests that the microstructure of cerebellar WM tracts is preserved (eg, normal axonal packing, diameter, and myelination) and that a malformed cerebellum does not cause a secondary alteration of the connecting WM tracts (at least detectable by our approach). This finding is important for the primary or secondary role of the cerebellum in the pathogenesis of cognitive and affective impairment in children with CH. Distinction between CA and CH is not difficult in theory but can be problematic or impossible in practice on the basis of a single examination. An accurate differentiation between CA and CH is important for a targeted diagnostic work-up, correct diagnosis, early institution of the correct therapy, prediction of the prognosis, and counseling of the family, including inheritance pattern and risk of recurrence. Our preliminary results suggest that FA values of the CTT may differentiate CA and CH on a single neuroimaging study. Our preliminary results, however, need to be validated in future studies, including larger cohorts of patients.

Limitations
This study was performed in the context of a clinical MR imaging examination. Due to the need for a short acquisition time, we were able to apply only 30 gradient directions. This number of directions is too low to qualify the technique as high-angular-resolution diffusion imaging. However, we believe that this number of directions is appropriate for a preliminary project to study the feasibility of advanced processing procedures with constrained spherical deconvolution in children with cerebellar pathologies. A higher number of gradient directions, measurement of DTI scalars along the white matter tracts (instead of 1 average value), and inclusion of additional white matter tracts (eg, spinocerebellar tracts) may provide additional important information and should be considered for future research studies, including a larger cohort of patients. The sample size is limited due to the inclusion criteria and the low prevalence of the included cerebellar pathologies in the pediatric population. However, the significant results, even in a small cohort of patients, are convincing.

CONCLUSIONS
Our study shows the feasibility of probabilistic tractography with constrained spherical deconvolution to reconstitute cerebellar tracts and the CST in children with morphologic cerebellar pathologies. In addition, our preliminary results show the potential utility of quantitative analysis of scalars of the cerebellar WM tracts in children with cerebellar pathologies such as CH and CA. Further studies with larger cohorts of patients are needed to validate the clinical significance of our preliminary results.

ACKNOWLEDGMENTS
We thank all children who took part in the study and their families.

REFERENCES
1. Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci 2008;34:51–61 CrossRef Medline
2. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do’s and don’ts of diffusion MRI. Neuroimage 2013;73:239–54 CrossRef Medline
3. Mori S, Wakana S, Nagae-Poetscher LM, et al. MRI Atlas of Human White Matter. Amsterdam: Elsevier; 2005
4. Rollins NK. Clinical applications of diffusion tensor imaging and tractography in children. Pediatr Radiol 2007;37:769–80 CrossRef Medline
5. Tournier JD, Calamante F, Connelly A. Determination of the appropriate b value and number of gradient directions for high-angular-resolution diffusion-weighted imaging. NMR Biomed 2013;26:1775–86 CrossRef Medline
6. Tournier JD, Yeh CH, Calamante F, et al. Resolving crossing fibers using constrained spherical deconvolution: validation using diffusion-weighted imaging phantom data. Neuroimage 2008;42:617–25 CrossRef Medline
7. Palesi F, Tournier JD, Calamante F, et al. Contralateral cerebellothalamo-cortical pathways with prominent involvement of associative areas in humans in-vivo. Brain Struct Funct 2015;220:3369–84 CrossRef Medline
8. Chokshi FH, Poretti A, Meoded A, et al. Normal and abnormal development of the cerebellum and brainstem as depicted by diffusion tensor imaging. Semin Ultrasound CT MR 2011;32:539–54 CrossRef Medline
9. Kamali A, Kramer LA, Frye RE, et al. Diffusion tensor tractography of the human brain cortico-ponto-cerebellar pathways: a quantitative preliminary study. J Magn Reson Imaging 2010;32:809–17 CrossRef Medline
10. Klingberg T, Vaidya C, Gabrieli JD, et al. Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. Neuroreport 1999;10:2817–21 CrossRef Medline
11. Saksena S, Husain N, Malik GK, et al. Comparative evaluation of the cerebral and cerebellar white matter development in pediatric age group using quantitative diffusion tensor imaging. Cerebellum 2008;7:392–400 CrossRef Medline
12. Leitner Y, Travis KE, Ben–Shachar M, et al. Tract profiles of the cerebellar white matter pathways in children and adolescents. Cerebellum 2015 Feb 4. [Epub ahead of print] CrossRef Medline
13. Bolshansker E. Cerebellar imaging: an important signpost in paediatric neurology. Childs Nerv Syst 2001;17:211–16 CrossRef Medline
14. Poretti A, Huisman TA, Scheer I, et al. Joubert syndrome and related disorders: spectrum of neuroimaging findings in 75 patients. AJNR Am J Neuroradiol 2011;32:1459–63 CrossRef Medline
15. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110–24 CrossRef Medline
16. Namavar Y, Barth PG, Kasher PR, et al. Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia. Brain 2011;134:143–56 CrossRef Medline
17. Widiasa E, Blaser S, Raybaud C. Diffusion tensor imaging of midline posterior fossa malformations. Pediatr Radiol 2006;36:310–17 CrossRef Medline
18. Huisman TA, Bosemani T, Poretti A. Diffusion tensor imaging for
brain malformations: does it help? Neuroimaging Clin N Am 2014; 24:619–37 CrossRef Medline
19. Bucci M, Mandelli ML, Berman JJ, et al. Quantifying diffusion MRI tractography of the corticospinal tract in brain tumors with deterministic and probabilistic methods. Neuroimage Clin 2013;3:361–68 CrossRef Medline
20. Poretti A, Boltschauer E, Loeneker T, et al. Diffusion tensor imaging in Joubert syndrome. AJNR Am J Neuroradiol 2007;28:1929–33 CrossRef Medline
21. Fiori S, Pannek K, Pasqualetti R, et al. Corticopontocerebellar connectivity disruption in congenital hemiplegia. Neurorehabil Neural Repair 2015;29:858–66 CrossRef Medline
22. Law N, Bouffet E, Laughlin S, et al. Cerebellar-thalamo-cerebral connections in pediatric brain tumor patients: impact on working memory. Neuroimage 2011;56:2238–48 CrossRef Medline
23. Jeong JW, Asano E, Juhasz C, et al. Quantification of primary motor pathways using diffusion MRI tractography and its application to predict postoperative motor deficits in children with focal epilepsy. Hum Brain Mapp 2014;35:3216–26 CrossRef Medline
24. Lui YW, Law M, Chacko-Mathew J, et al. Brainstem corticospinal tract diffusion tensor imaging in patients with primary posterior fossa neoplasms stratified by tumor type: a study of association with motor weakness and outcome. Neurosurgery 2007;61:1199–1207; discussion 1207–08 CrossRef Medline
25. Kovanlikaya I, Firat Z, Kovanlikaya A, et al. Assessment of the corticospinal tract alterations before and after resection of brainstem lesions using diffusion tensor imaging (DTI) and tractography at 3T. Eur J Radiol 2011;77:383–91 CrossRef Medline
26. Law N, Greenberg M, Bouffet E, et al. Visualization and segmentation of reciprocal cerebrocerebellar pathways in the healthy and injured brain. Hum Brain Mapp 2015;36:2615–28 CrossRef Medline
27. Rizzo G, Tonon C, Valentino ML, et al. Brain diffusion-weighted imaging in Friedreich’s ataxia. Mov Disord 2011;26:705–12 CrossRef Medline
28. Pagani E, Ginestrioni A, Della Nave R, et al. Patterns of fractional anisotropy changes in white matter of cerebellar peduncles distinguish cerebellar ataxia syndromes. Neuroimage 2009;47(suppl 2):T72–81 CrossRef Medline
29. Poretti A, Boltschauer E, Doherty D. Cerebellar hypoplasia: differential diagnosis and diagnostic approach. Am J Med Genet C Semin Med Genet 2014;166C:211–26 CrossRef Medline
30. Yoon B, Kim JS, Lee KS, et al. Early pathological changes in the cerebellum of patients with pure cerebellar syndrome demonstrated by diffusion-tensor imaging. Eur Neurol 2006;56:166–71 CrossRef Medline
31. Prakash N, Hageman N, Hua X, et al. Patterns of fractional anisotropy changes in white matter of cerebellar peduncles distinguish spinocerebellar ataxia-1 from multiple system atrophy and other ataxia syndromes. Neuroimage 2008;47(suppl 2):T72–81 CrossRef Medline
32. Poretti A, Boltschauer E, Doherty D. Cerebellar hypoplasia: differential diagnosis and diagnostic approach. Am J Med Genet C Semin Med Genet 2014;166C:211–26 CrossRef Medline
33. Poretti A, Wolf NJ, Boltschauer E. Differential diagnosis of cerebellar atrophy in childhood. Eur J Paediatr Neurol 2008;12:155–67 CrossRef Medline
34. Boltschauer E. Cerebellar hypoplasias. Handb Clin Neurol 2008;87:115–27 CrossRef Medline
35. Boltschauer E. Cerebellum-small brain but large confusion: a review of selected cerebellar malformations and disruptions. Am J Med Genet A 2004;126A:376–85 CrossRef Medline
36. Pannk K, Raffelt D, Bell C, et al. HOMOR: higher order model outlier rejection for high b-value MR diffusion data. Neuroimage 2012;63:835–42 CrossRef Medline
37. Pannk K, Boyd RN, Fiori S, et al. Assessment of the structural brain network reveals altered connectivity in children with unilateral cerebro-palaeo dysplasia due to periventricular white matter lesions. Neuroimage Clin 2014;4:84–92 CrossRef Medline
38. Jenkins M, Beckmann CF, Behrens TE, et al. FSL. Neuroimage 2012;62:782–90 CrossRef Medline
39. Kanai R, Rees G. The structural basis of inter-individual differences in human behaviour and cognition. Nat Rev Neurosci 2011;12:231–42 CrossRef Medline
40. Johansen-Berg H. Behavioural relevance of variation in white matter microstructure. Curr Opin Neurol 2010;23:351–58 CrossRef Medline
41. Song SK, Sun SW, Ramsbottom MJ, et al. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 2002;17:1429–36 CrossRef Medline
42. Pierpaoli C, Barnett A, Pajevic S, et al. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. Neuroimage 2001;13:1174–85 CrossRef Medline
43. Namavar Y, Barth PG, Poll-The BT, et al. Classification, diagnosis and potential mechanisms in pontocerebellar hypoplasia. Orphanet J Rare Dis 2011;6:50 CrossRef Medline
44. Barth PG, Aronica E, de Vries L, et al. Pontocerebellar hypoplasia type 2: a neuropathological update. Acta Neuropathol 2007;114:373–86 CrossRef Medline
45. Takashashi J, Arai H, Nabatame S, et al. Neuroradiologic features of CASK mutations. AJNR Am J Neuroradiol 2010;31:1619–22 CrossRef Medline
46. Najm J, Horn D, Wimmlinger I, et al. Mutations of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum. Nat Genet 2008;40:1065–67 CrossRef Medline
47. Kuo TY, Hong CJ, Chien HL, et al. X-linked mental retardation gene CASK interacts with Bcl11A/CTIP1 and regulates axon branching and outgrowth. J Neurosci Res 2010;10:88:2364–73 CrossRef Medline
48. Anderson GW, Goebel HH, Simonati A. Human pathology in NCL. Biochim Biophys Acta 2013;1832:1807–26 CrossRef Medline
49. Jadav RH, Sinha S, Yasha TC, et al. Mutations of CASK cause a characteristic MRI finding in congenital disorders of glycosylation type 1a. AJNR Am J Neuroradiol 2012;33:2062–67 CrossRef Medline
50. Friston K. Ten ironic rules for non-statistical reviewers. Neuroimage 2012;61:1300–10 CrossRef Medline