Diffusion tensor MRI shows abnormal brainstem crossing fibers associated with ROBO3 mutations

Abstract—Horizontal gaze palsy with progressive scoliosis (HGPPS) is caused by mutations in the ROBO3 gene, critical for the crossing of long ascending medial lemniscal and descending corticospinal tracts in the medulla. Diffusion tensor imaging in a patient with HGPPS revealed the absence of major pontine crossing fiber tracts and no decussation of the superior cerebellar peduncles. Mutations in the ROBO3 gene lead to a widespread lack of crossing fibers throughout the brainstem.

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Horizontal gaze palsy with progressive scoliosis (HGPPS; OMIM 607313) is a rare syndrome of absent horizontal gaze and severe progressive scoliosis from birth. The occurrence of HGPPS in consanguineous families suggests a recessive inheritance pattern. The gene responsible for HGPPS was recently identified as ROBO3, which encodes a protein that shares homology with the roundabout family of transmembrane receptors important in axon guidance and neuronal migration.

Although subjects with HGPPS seem neurologically normal aside from their inability to move their eyes horizontally, there is a striking brainstem malformation, with markedly diminished size and a bifid appearance of the medulla oblongata (“butterfly medulla”). The extraocular muscles and their larger motor nerves are normal in HGPPS. However, brainstem evoked potential studies demonstrate that the corticospinal and dorsal column fibers have exclusively ipsilateral projections. The unusual appearance of the medulla and abnormal functional results suggest that sensorimotor projections do not cross the midline in HGPPS. Similarly, in mice deficient in Robo3 (also called Rig1), there is a complete absence of commissural axon crossing of the floor plate throughout the hindbrain and spinal cord.

Although midline crossing defects in the hindbrain are shared between humans with HGPPS and mice with knockout of the ROBO3 gene, the developmental defects in the mouse seem to be more profound than those in humans, because the mutant mouse dies soon after birth, whereas patients with HGPPS are remarkably neurologically intact. The role of ROBO3 in human neurodevelopment is not fully understood because of the rarity of HGPPS and the lack of pathologic specimens for direct evaluation of specific brainstem structures and fiber tracts.

Previously, in vivo structural brain imaging of patients with HGPPS has been limited to standard T1- and T2-weighted MRI studies. Diffusion tensor imaging (DTI) can be used to identify specific fiber tracts and their directionality and is useful in assessing brainstem structures. We now report results of DTI in a subject with HGPPS. Findings include the absence of major crossing pathways within the pons and midbrain.

Methods. We studied a 19-year-old woman with HGPPS who is one of three affected siblings from Family AX. Genetic studies revealed a homozygous frameshift mutation 2310 + 1C in exon 15. DTI data were also obtained from a 33-year-old male control.

Magnetic resonance scans were obtained with a Siemens Sonata 1.5-T scanner (Erlangen, Germany) using the following scanning protocols: A T1-weighted three-dimensional volume (sagittal 1.2 mm, 124 slices, field of view (FOV) 24, matrix 256 × 256, inversion recovery pulse sequence (IR) prepaped time from inversion (TI) 400 milliseconds). Diffusion weighted images for DTI analysis were obtained with the following parameters: spin echo planar imaging repetition time (TR) 5,000, echo time (TE) 83, 62 axial slices, 2 mm thickness, FOV 24, matrix 128 × 128, diffusion gradients applied in six independent nonlinear directions, four b values (0, 400, 800, 1,600 seconds/mm²). Five separate acquisitions were performed.

For each DWI acquisition set, the brain identified in each volume was spatially aligned to the b = 0 image using Automated Image Registration (AIR) with a 12-parameter affine model. After this, each acquisition’s b = 0 volume was aligned to the first acquisition’s b = 0 volume, resliced into the b = 0 space of the first acquisition, and signal averaged.

The T1-weighted structural volume that had been resampled into the same 2-mm axial slice thickness as the DTI data were aligned with the computed tensors. The symmetric 3 × 3 diffusion tensor was computed for each voxel using a multivariate linear regression method. Fractional anisotropy and lattice index images

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were also generated. The set of eigenvectors obtained from a diagonalization of the diffusion tensor was visualized using a directionally encoded color (DEC) method. The DEC image was scaled by the lattice index, which measures the local coherence of the tensor data, and was displayed using BrainSuite2.0 (http://www.loni.ucla.edu/Software/).

Structural and tensor weighted MRI data of the patient with horizontal gaze palsy were compared with data obtained from the normal control and cross-correlated with published anatomic data on brainstem cytoarchitecture and fiberarchitecture. In addition, reference was made to previously published fiber tracts in normal subjects depicted with DTI.

Results. General physical examination of the 19-year-old right-handed woman revealed severe scoliosis. She had absent horizontal gaze, but otherwise normal strength, sensation, and coordination. The T1-weighted MRI scan reveals the characteristic "butterfly" appearance of the medulla. The basis pontis is smaller along with all three cerebellar peduncles. The volume of the midbrain tegmentum is decreased in the HGPPS subject as well (figures 1 and 2).

Diffusion tensor imaging reveals other tract specific abnormalities in the HGPPS patient. At the midbrain level, the tensor images of the patient demonstrate the absence of the decussation of the superior cerebellar peduncles, seen as an area of red in the control subject (figure 3C). At the pontine level (figure 3, A and B) there is an absence of the major crossing fibers. In the control subject, there is a large red band in the midbody of the pons representing fibers oriented in a medial–lateral direction not seen in the HGPPS patient. The complete absence of these crossing fibers is demonstrated in the axial image, sagittal and coronal views (figure 3, A, B, and D). The midportion of the basis pontis of the patient with HGPPS has some fibers oriented in a medial–lateral direction (displayed as red) consistent with the pontine crossing fibers that normally arise from pontine nuclei and project to the contralateral cerebellum via the middle cerebellar peduncle. Whether these fiber tracts that are oriented in the medial–lateral direction at this level are actually crossing the midline or are just touching cannot be determined from these data, which reveals orientation but does not delineate individual fiber tract trajectories.

The DTI images of the supratentorial region appeared normal in the subject with HGPPS. The corpus callosum exhibited normal shape and fiber tract orientation. The major white matter pathways of the brain were well formed and normally oriented (figure E-1 on the Neurology Web site at www.neurology.org).

Discussion. Previous studies of humans with HGPPS have demonstrated brain structural and functional abnormalities consistent with the absence of the normal decussation pattern of the major sensory and motor pathways within the medulla. Diffusion tensor imaging in the current subject revealed previously unrecognized additional disruptions in the midline crossing of other fiber tracts in the pons and midbrain including the trapezoid body and the superior cerebellar peduncles. The widespread abnormalities of hindbrain crossing fibers identified by DTI in human HGPPS are reminiscent of the abnormalities in mice with knockout of the Robo3 gene. A recent application of DTI with tract tracing in a patient with a clinical syndrome similar to HGPPS demonstrated a partial decussation of the corticospinal tracts. However, interpretation of these results is limited by the absence of genetic verification of ROBO3 mutations and functional correlation in this individual. Whether there is
variability in the phenotypic expression of mutations in the ROBO3 gene awaits further verification. The spatial resolution of our DTI data did not allow for identification of the decussation of the corticospinal tracts in our patient with HGPPS or the control.

Despite the extensive neuroanatomic derangements present in HGPPS, patients have preserved motor and sensory function and coordination. They do not demonstrate the severe ataxia and apraxia seen in Joubert syndrome, another developmental disorder with uncrossed corticospinal tracts along with other abnormalities. Further studies of functional organization in conjunction with high-resolution structural imaging of fiber tracts are needed in human HGPPS.

References