Diffusion Tensor Imaging and Fiber Tractography in Syntelencephaly

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ABSTRACT

Syntelencephaly or the middle interhemispheric variant of holoprosencephaly is a rare subtype of holoprosencephaly and consists of a nonseparation of the posterior frontal and parietal regions of both cerebral hemispheres. We report conventional MR imaging, diffusion tensor imaging, and fiber tractography findings of a girl with syntelencephaly and discuss the information that diffusion tensor imaging and fiber tractography may add to conventional MR imaging in this rare brain malformation.

INTRODUCTION

DTI is an advanced MR imaging technique that allows the investigation of white matter organization and microstructure in vivo. DTI combines information about the 3D direction of diffusion of water in space and allows estimating the 3D diffusion profile within each voxel. The 3D diffusion profile can be represented mathematically as a symmetric $3 \times 3$ matrix of numbers, the so-called “tensor of diffusion.” From this approximation, the principal direction of diffusion within the brain can be determined. This estimates the predominant direction of axonal projection within a voxel and may be color-coded. Information about the main direction and magnitude of diffusion from neighboring voxels may be combined for FT, which is a powerful postprocessing tool that allows graphic reconstruction of the white matter pathways. Therefore, DTI and FT are suitable MR imaging tools for studying the internal neuroarchitecture of the abnormally developing brain noninvasively. Assessing the size and 3D orientation of white matter tracts, which may be affected in brain malformations, DTI and FT give insights into many malformations, such as Joubert syndrome, pontine tegmental cap dysplasia, or horizontal gaze palsy and progressive scoliosis.

We describe a young girl with syntelencephaly and present the conventional MR imaging, DTI and FT findings.

CASE REPORTS

A 2-year-old girl was referred to our hospital because of global developmental delay. She is the third child of healthy, nonconsanguineous parents. Her 2 older brothers are healthy. The family history was negative for genetic abnormalities or syndromes. She was born at term after an uneventful pregnancy (particularly no maternal exposure to drugs, diabetes mellitus, or nicotine abuse). At 2 years of age, she could climb steps on her knees, but she did not walk without support. She had a vocabulary of approximately 10 words but did not use any multiple word phrases. She never had epileptic seizures. Neurologic examination did not show focal neurologic deficits in the context of global developmental delay. No facial dysmorphic features were seen.

MR imaging of the brain was performed on a 1.5T scanner (Avanto; Siemens, Erlangen, Germany). The imaging sequences included 3D T1-weighted images, axial T2-weighted images, FLAIR sequences, and DTI.
Conventional MR imaging revealed complete absence of the body of the corpus callosum but the presence of the callosal genu and splenium (Fig 1A–C). The septum pellucidum was absent (Fig 1D). The posterior frontal lobes and part of the parietal regions (postcentral gyrus and superior parietal lobule) were fused, with continuation of both the gray and white matter across the midline (Fig 1A, -C). At this level, the falx and the interhemispheric fissure could not be identified and the cortex around the interhemispheric fissure appeared dysplastic (Fig 1A, -C). Otherwise, no dysplastic cortex or heterotopic gray matter was found. The Sylvian fissures were normal and not abnormally connected across the midline over the vertex as previously reported in some patients with syntelencephaly. The basal ganglia and thalami were separated, and the hypothalamus and midbrain had a normal morphology (Fig 1A, -B). The pituitary gland and all the structures in the posterior fossa appeared normally formed (Fig 1A). The ventricles appeared normal; no dorsal cyst was present. Examination of the flow voids demonstrated an apparent single right anterior cerebral artery, likely compatible with a single azygous artery (not shown).

DTI consisted of a single-shot, spin-echo, echo-planar balanced diffusion-weighted sequence. Diffusion encoding was applied along 21 directions in space. Images were acquired by using b-values of 0 seconds/mm² and 800 seconds/mm²; TR = 7100 ms; TE = 84 ms; section thickness = 2.5 mm; FOV = 240 × 240 mm; matrix = 192 × 192. DTI postprocessing was performed off-line by using DTIStudio software (H. Jiang and S. Mori, Johns Hopkins University, Baltimore, Maryland; www.MriStudio.org). All images were coregistered to one another and corrected for eddy current and subject motion by using a 12-mode affine transformation of automated image registration. Subsequently, color-coded FA maps were generated. Finally, FT reconstruction was performed by using the Fiber Assignment by Continuous Tracking Algorithm in TrackVis software (Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts). FT propagation was terminated when the turning angles between the primary eigenvectors of neighboring voxels were >35°. FT was performed by manually positioning seed points within the following: 1) the genu and splenium of the corpus callosum, 2) the communicating white matter between the fused parts of the cerebral hemispheres, and 3) the IFO (the region of interest to delineate the IFOs was placed in the green [anteroposterior orientation] voxels located below the external capsule on a coronal section of the color-coded FA maps at the posterior edge of the genu of the corpus callosum, where the IFO is expected to be located). A DTI atlas was used to guide placement of the seed points.

Axial color-coded FA maps showed a thick bundle of red (transversely oriented) white matter fibers in the expected location of the body of the corpus callosum (Fig 1E,-H). The cingulum bundles were laterally displaced at the level of the fused hemispheres (Fig 1F). CST and ML tracts were present and not fused at the level of the brain stem (not shown). FT revealed that these transverse fibers connected the fused regions of the posterior frontal and parietal lobes (Fig 2B, -E). The AC was present (Fig 1A, -E). FT also showed that the fibers projecting to both anterior frontal lobes and occipitotemporal lobes crossed the midline at the present part of the genu and splenium of the corpus callosum, respectively (Fig 2A, -D). The IFO could be easily identified (Fig 2C, -F) and partially connected the fibers...
projecting to the occipitotemporal lobes with those project-
ing to the anterior frontal lobes (Fig 2A, C, and D). The MCP appeared to be normal in size (not shown).

**DISCUSSION**

Holoprosencephaly is a complex human brain malforma-
tion resulting in nonseparation of midline structures due to incomplete cleavage of the prosencephalon (“embryonic forebrain”) into right and left hemispheres. This embryologic process is normally complete by the fifth week of gestation. The etiology of HPE is very heterogeneous and includes environmental and genetic causes. Maternal insulin-dependent diabetes mellitus and maternal alcoholism with a risk that cumulates with smoking are the only formally recognized environmental risk factors, but HPE has also been reported in association with prenatal drug exposure such as retinoic acid and cholesterol biosynthesis inhibitors and with prenatal infections due to cytomegalovirus, toxoplasma, and rubella. Genetic causes include chromosomal abnormalities (with a higher prevalence observed in trisomy 13 and 18 and triploidy), several multiple malformation syndromes with a normal karyotype (eg, Smith-Lemli-Opitz, Pallister-Hall, and velocardiofacial syndromes), and mutations in additional genes outside a well-defined syndrome (eg, sonic hedgehog, ZIC2, SIX3 and TG-interacting factor). In patients with HPE, not only is the brain involved but the eyes (eg, cyclopia, an- or microphthalmia, and colobomas), skull (eg, hypotelorism, fused orbits), nose (eg, proboscis, single nares, flat nose, and stenosis of the pyriform sinus), teeth (eg, fused or missing teeth, single maxillary central incisor), lip (uni- or bilateral and median cleft lip), and palate (uni- or bilateral and median cleft palate) may also be affected. Additionally, neural tube defects, digital anomalies, club feet, congenital heart defects, and abnormal genitalia have been reported in association with HPE.

HPE has traditionally been classified into 3 grades of increasing severity based on neuroanatomic abnormalities: 1) lobar HPE, in which the cerebral hemispheres are rather well-developed and separated (including thalamic nuclei), with rudimentary formation of the frontal horns of the lateral ventricles without separation of only the most rostral/ventral parts of the neocortex, and with absence of the corpus callosum in the affected region; 2) semilobar HPE, with lack of separation of the anterior hemispheres and incomplete separation of the deep gray matter nuclei, but separation of some portions of the posterior hemispheres, resulting in the presence of the posterior horns and trigones of the lateral ventricles and of the splenium of the corpus callosum; and 3) alobar HPE, the most severe form, with a complete or nearly complete lack of separation of the cerebral hemispheres inclusive of the basal ganglia, thalami, and hypothalami; a single midline forebrain ventricle (monoventricle), which often communicates with a dorsal cyst; and a complete absence of the interhemispheric fissure, falx cerebri, and corpus callosum. Additionally, there is another rare and milder form called middle interhemispheric variant or syntelencephaly, which was first described in 1993.

Syntelencephaly consists of a nonseparation of the pos-
terior frontal and parietal regions of both cerebral hemi-
spheres, while the basal forebrain, anterior part of the frontal lobes, and occipital lobes are well-separated. Additional neuroanatomic characteristics of syntelencephaly include a normally formed genu and splenium of the corpus callosum, but absence of the callosal body; incomplete separation of the caudate nuclei and thalami, but normal complete separation of the hypothalamus and lenti-
form nuclei; nearly vertical orientation of the Sylvian fissures, which are abnormally connected across the midline over the vertex of the brain; subcortical gray matter heterotopia or cortical dysplasia in approximately 30% of the patients; and abnormality of the anterior cerebral vessels with a single azygous artery.\textsuperscript{14}

We are not aware of previous DTI/FT studies in syntelencephaly. In our patient, DTI confirmed the fusion of the posterior frontal and parietal lobes, showing a thick bundle of red (transversely oriented) white matter fibers that are crossing the midline and run from one hemisphere to the other. With FT, the projection of these fibers onto the hemispheric cerebral cortex delineates the fused regions well. Because these fibers are connecting 2 parts of the fused hemispheres and they are not connecting distant functional centers, they are not commissural fibers, but just short-distance connecting white matter tracts. On the other hand, the white matter fibers that originate from cortical regions located anteriorly and posteriorly to the fused ones are running to the other hemisphere through the genu and splenium of the corpus callosum, respectively. White matter fibers from the temporal lobes are running through the splenium of the corpus callosum and show that in syntelencephaly, the temporal lobes are well-separated. The normal anatomy of the temporal lobes is supported by the depiction of the AC and IFO on both sides. The AC is a compact, transversely oriented white matter fiber bundle interconnecting olfactory structures (anterior limb) and the anterior portions of the middle and inferior temporal gyri (posterior limb). The IFO consists of fibers that connect the lateral parts of the frontal lobe with the inferior temporal and medial and lateral occipitotemporal gyri and the occipital lobe. In our patient, both IFOs were not fused. Complete separation of the IFOs is probably present in lobar HPE too, whereas bilateral fusion of the IFOs has been reported in semilobar HPE.\textsuperscript{14} In semilobar HPE, DTI and FT also revealed absent demarcation between the inferior and superior longitudinal fasciculus, thickened and dysplastic fornices, and a projection of the CST anteriorly toward the expected location of the motor cortex.\textsuperscript{14}

Abnormalities of the CST have also been reported in other types of HPE. In patients with alobar HPE, the CST was reported to be absent bilaterally, and in another patient with semilobar HPE, the CST was not identifiable at the level of the medulla oblongata.\textsuperscript{15} The dimensions of the CST and MCP have been reported to be associated with the HPE type and neurologic impairment.\textsuperscript{15} In our patient, the CST, ML, and MCP appeared normal in size at the level of the brain stem. This appearance correlates well with the relatively mild neurologic deficit of our patient. Probably the dimension not only of the CST and MCP but also of other white matter tracts and generally their presence and separation are responsible for the milder neurologic impairments in lobar HPE and syntelencephaly compared with semilobar and particularly alobar HPE. Of course, further DTI studies in larger cohorts with all types of HPE could provide a more complete picture of normal and abnormal white matter tracts in HPE and could reveal clear correlations between anatomy and function.

Of course, some basic technical limitations of DTI and FT reproducibility have to be considered because they may affect the interpretation of results. Pulsation and geometric warping artifacts due to vessels and brain-air-bone interfaces, respectively, may reduce the image quality, particularly in the infratentorial regions. High spatial resolution, such as cubic voxels of 2.5 mm on a side or smaller, is needed for a detailed visualization of small white matter tracts. Different acquisition DTI parameters, scanners, and/or magnetic field strength may bias comparison of data. FT limitations are mostly due to discrepancies between the scale of the axonal diameter and the imaging voxel size (low spatial resolution), the noise contained in the diffusion data, and image artifacts.\textsuperscript{3} Additionally, FT performs poorly in regions with multiple populations or crossing fibers because of the assumption that in each voxel, all fibers are well-described by a single orientation. This may result in tracking of nonexistent pathways or ineffective tracking of existing tracts. To avoid the inclusion of spurious fibers, protocols using multiple regions of interest have been created to reconstruct major white matter tracts with high reproducibility.\textsuperscript{16} In brain malformations, however, it may be difficult to apply these protocols due to abnormal brain anatomy. Of high importance in performing FT is the adequate setting of threshold values of FA and trajectory angles for FT termination, because more fibers may be falsely generated or tracts may be ignored, depending on the selected thresholds. High FA threshold values typically demonstrate fewer fibers, while low FA threshold values show more fiber connections. Moreover, a large threshold for the deflection angle may result in the depiction of more fibers connecting distant areas. Finally, multitemporal DTI may further resolve crossing fibers within 1 voxel.

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