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Diffusion Tensor Imaging of Aicardi Syndrome

Michael Wahl, MS[*,†,1], **Zoe A. Strominger, AB**[*,1], **Mari Wakahiro, MSW**[*], **Rita J. Jeremy, PhD**[‡], **Pratik Mukherjee, MD PhD**[†], and **Elliott H. Sherr, MD PhD**[*]

[*]Department of Neurology, University of California, San Francisco

[†]Department of Radiology, University of California, San Francisco

[‡]Department of Pediatrics, University of California, San Francisco

Abstract

Aicardi syndrome is a congenital neurodevelopmental disorder associated with significant cognitive and motor impairment. Diffusion Tensor Imaging was performed on two subjects with Aicardi syndrome, as well as on two matched subjects with callosal agenesis and cortical malformations, but not a clinical diagnosis of Aicardi syndrome. Whole brain three-dimensional fiber tractography was performed, and major white matter tracts were isolated using standard tracking protocols. One Aicardi subject demonstrated an almost complete lack of normal cortico-cortical connectivity, with only the left inferior fronto-occipital fasciculus recovered by diffusion tensor tractography. A second Aicardi subject showed evidence of bilateral cingulum bundles and right uncinate fasciculus, but other cortico-cortical tracts were not recovered. Major subcortical white matter tracts, including corticospinal, pontocerebellar, and anterior thalamic radiation tracts, were recovered in both Aicardi subjects. In contrast, diffusion tensor tractography analysis on the two matched control subjects with callosal agenesis and cortical malformations recovered all major intrahemispheric cortical and subcortical white matter tracts. These results reveal a widespread disruption in the corticocortical white matter organization of individuals with Aicardi syndrome. Furthermore, such disruption in white matter organization appears to be a feature specific to Aicardi syndrome, and not shared by other neurodevelopmental disorders with similar anatomic manifestations.

Introduction

Aicardi syndrome, a congenital neurodevelopmental disorder associated with severe cognitive and motor impairment, is defined by the diagnostic triad of corpus callosum dysgenesis, chorioretinal lacunae and infantile spasms [1,2]. Other common neurological findings include polymicrogyria, periventricular and subcortical heterotopia, and choroid plexus papillomas [3]. Though the anatomical features of Aicardi have been well described by conventional neuroimaging [4], little is known about the underlying white matter structural organization of individuals with Aicardi syndrome.

Communications should be addressed to: Dr. Elliott Sherr; Department of Neurology; University of California, San Francisco; 505 Parnassus Ave, Box 0114; San Francisco, CA 94143-0114. sherre@neuropeds.ucsf.edu, For communication during review and before publication: Phone: (415) 514-9306; Fax: (415) 476-2723 .
[1]Both authors contributed equally to this work.

Diffusion Tensor Imaging (DTI) is an MRI imaging modality that characterizes the microstructural organization of major white matter tracts by measuring the degree of anisotropic diffusion of water within the brain [5]. Since water diffuses preferentially along the axis of axonal fiber bundles, the direction of greatest diffusion indicates the course of major white matter fibers, while the degree of diffusion anisotropy is an indication of white matter microstructural integrity. In recent years DTI has been increasingly used to investigate neurodevelopmental disorders, including agenesis of the corpus callosum [6,7], horizontal gaze palsy with progressive scoliosis [8,9], pontine tegmental cap dysplasia [10,11], and holoprosencephaly [12,13]. We present DTI findings for two subjects with Aicardi syndrome, revealing substantial alterations to white matter organization.

Methods

Patient Histories

Aicardi subject 1 is a 10-year-old girl who was born at 38 weeks to a 31-year-old gravida 2 mother. Parents were nonconsaguinous. A 30-week ultrasound suggesting hydrocephalus resulted in a postnatal MRI, which revealed agenesis of the corpus callosum. At birth the child's weight was 3374g. The child remained in the hospital for 7 days because of jaundice.

Bilateral chorioretinal lacunae were documented at 3 months. The left macula lacunae were more severe than the right and she had left eye esotropia. Magnetic resonance imaging revealed complete callosal agenesis and type II interhemispheric cysts [14], which were subsequently fenestrated. She also had colpocephaly, bilateral subependymal nodular heterotopia, bilateral subcortical heterotopia, left frontal polymicrogyria, and an absent anterior commissure. In the posterior fossa, arachnoid cysts and cerebellar dysplasia were noted.

The child developed infantile spasms in the first few months of life and these occurred two times per day upon waking from sleep. She later developed tonic seizures, more severe clonic seizures, and gelastic seizures. Her antiepileptic regimen included clorazepate, lamotrigine, levetiracetam, and diazepam rectal gel as needed. She had spastic quadriplegic cerebral palsy. In addition, she was nonverbal, did not signal, and did not follow commands, but clearly responded to her name. She laughed and smiled frequently in response to specific stimuli, used eye contact, and responded to attention. Because of her severe intellectual impairment, standardized intelligence testing was not performed.

We conducted an analysis of chromosomal copy number variation using a custom NimbleGen array with 380,000 oligos spanning the X chromosome, comparing DNA from each proband to their respective mothers. This analysis did not reveal any clinically significant copy number variations in either patient.

Aicardi subject 2 is a 34-year-old woman who was born to a 29-year-old primigravida mother. Parents were nonconsanguineous and later had 2 healthy children. The patient was delivered by normal spontaneous delivery and at birth weighed 2410g. She was not diagnosed with Aicardi syndrome until the age of 6 years, when her lacunae were identified, although infantile spasms began at 6 weeks of age.

Ophthalmological findings included chorioretinal lacunae, bilateral optic nerve colobomas, and chronic open angle glaucoma. Magnetic resonance images were limited but revealed partial absence of the corpus callosum, colpocephaly, absence of the septum pellucidum, and absence of the anterior commissure. She was hypothyroid and born with hemivertebrae, requiring a spinal fusion at the age of 9.

In the first month of life, the mother noticed her child's abnormal tone and motor development. In addition to infantile spasms by 2 months, she developed atonic seizures. These later disappeared and she developed flexor spasms and generalized tonic clonic seizures. Her antiepileptic regimen included carbamazepine, gabapentin, levetiracetam, and diazepam rectal gel as needed. She had spastic cerebral palsy but began to walk at 5 years and used her right hand only with partial thumb opposition. She was also nonverbal and did not respond to her name. She did not signal on her own but laughed in response to specific stimuli, recognized faces, responded to attention, and used eye gaze and touch to communicate needs. Because of her severe intellectual impairment, standardized intelligence testing was not performed.

For comparison purposes, subjects with callosal dysgenesis and associated cortical malformations, such as heterotopia and/or polymicrogyria, who had undergone a similar DTI protocol were retrospectively identified. To compare with Aicardi subject 1, an eight year-old male was identified with complete callosal agenesis and subcortical and periventricular heterotopia. This control subject had an intelligence quotient (IQ) of 70, as measured by the Wechsler Abbreviated Scale of Intelligence (WASI). For comparison with Aicardi subject 2, a 34 year-old male with partial callosal agenesis, periventricular heterotopia and polymicrogyria, was identified. This control subject had obsessive-compulsive disorder and an IQ of 90, measured by the WASI. These subjects will be referred to as control subjects 1 and 2, respectively.

Imaging

All subjects underwent MR imaging at our institution, including high resolution T1-weighted structural imaging and DTI at 3 Tesla. For subject 1, DTI was performed with 19 diffusion-encoding directions, TR/TE = 11500/68, with 2.2-mm axial sections, in-plane resolution of 2.2 × 2.2 mm, and a diffusion-weighting strength of b = 1000 s/mm^2. For Aicardi subject 2, DTI was performed with 55 diffusion-encoding directions, TR/TE = 7000/65, with 1.8-mm axial sections, in-plane resolution of 1.8 × 1.8 mm, and a diffusion-weighting strength of b = 1000 s/mm^2. Due to subject movement, the T1-weighted images for subject 2 were of low quality and not included in the study.

Control subject 1 underwent DTI imaging at 3T with 25 diffusion-encoding directions, TR/TE = 11000/81, with 2.4-mm axial sections, in-plane resolution of 2.2 × 2.2 mm, and a diffusion-weighting strength of b = 1000 s/mm^2. For control subject 2, a 55 diffusion-encoding direction DTI scan was obtained with identical acquisition parameters as those used for subject 2.

DTI datasets were corrected for motion and eddy current artifact using a linear image registration tool [15]. Color fractional anisotropy (FA) maps were then generated to visualize white matter organization using DtiStudio v2.4 software (http://www.mristudio.org) as described elsewhere [16]. Three-dimensional whole brain fiber tractography was performed, using a deterministic streamline algorithm [17]: tracts were initiated from all voxels with a fractional anisotropy greater than 0.2, and terminated at voxels with a fractional anisotropy less than 0.3, or a turning angle between adjacent voxels of greater than 50°. Major white matter tracts were isolated by manually drawn regions of interest (ROIs) using standard protocols [18]. For verification purposes, an additional tracking procedure was performed with less stringent fractional anisotropy thresholds, such that tracts were initiated from all voxels with a fractional anisotropy greater than 0.15, and terminated at voxels with a fractional anisotropy less than 0.15 or a turning angle of greater than 50°.

Results

Anatomical abnormalities evident on conventional imaging are discussed in the patient histories, with representative T1-weighted structural images shown in Figure 1 (A,D). Because of the absence of speech or comprehension in both patients, we initially assayed the integrity of the arcuate fasciculus (superior longitudinal fasciculus) by DTI. On DTI color fractional anisotropy images we noted bilaterally absent or severely diminished longitudinal fibers in the expected location of all domains of the superior longitudinal fasciculus in both Aicardi subjects (Fig. 1 B,C). In addition, the arcuate fasciculus portion of the superior longitudinal fasciculus was not recovered by DTI tractography in either subject. In contrast, the superior longitudinal fasciculus was clearly visible on DTI colormaps for both control subjects with callosal agenesis and cortical malformations (Fig. 1 E,F), and the arcuate fasciculus was successfully tracked in both control subjects, though only the left arcuate fasciculus could be tracked for control subject 2.

Since other white matter structures consist of multiple major white matter tracts, the presence of other white matter tracts could not be determined from inspection of DTI color FA images alone. However, further analysis with DTI tractography revealed a broad-based white matter disruption in the Aicardi subjects, as the vast majority of tracts were not recovered. While a right inferior fronto-occipital fasciculus (IFO) was recovered in Aicardi subject 1, there was no evidence of any other cortico-cortical connectivity, including left inferior fronto-occipital fasciculus, bilateral cingulum bundles, inferior longitudinal fasciculus (ILF), and uncinate fasciculus (Fig 2 A,B). In contrast, Probst Bundles, aberrant longitudinal white matter tracts found commonly in individuals with callosal agenesis [19,20], were readily identified bilaterally and tracked in Aicardi subject 1 (Fig 2 A,B). The Probst Bundles were found to connect frontal lobes with occipital and temporal lobes, although the precise sites of origin and termination of these tracts were difficult to ascertain, due to the complex structure of the white matter through which they pass. Probst Bundles were not identified in Aicardi subject 2, who instead showed evidence of bilateral cingulum bundles and the right uncinate fasciculus, but a lack of other cortico-cortical tracts (Fig 2, C,D).

As previously described, DTI tractography was performed on subjects with callosal agenesis and associated cortical malformations, but who did not have a clinical diagnosis of Aicardi syndrome. An individual with complete callosal agenesis with both subcortical and periventricular heterotopia, matched by age and scan quality to Aicardi subject 1, demonstrated the presence of all major cortical and subcortical white matter tracts (Fig 2 E,F). Similarly, an individual with partial callosal agenesis with periventricular heterotopia and polymicrogyria, matched by age and scan quality to Aicardi subject 2, demonstrated the presence of all major cortical and subcortical tracts, with the exception of the right arcuate fasciculus (Fig 2 G,H).

While cortico-cortical tracts were significantly disrupted in both Aicardi subjects, the major cortico-subcortical tracts, including the corticospinal, pontocerebellar and anterior thalamic radiation fibers were recovered in both subjects (Fig 3 A-D), and appeared grossly normal in size and orientation. Similarly, both control subjects demonstrated grossly intact subcortical white matter tracts (Fig 3 E-H).

Discussion

Our data support the hypothesis that cortical white matter organization is profoundly disrupted in two individuals with Aicardi syndrome. In both subjects we note greatly diminished cortico-cortical connectivity, with only the right inferior fronto-occipital

fasciculus, and bilateral Probst bundles, present in one subject, and bilateral cingulum bundles and right uncinate fasciclus present in another. Subcortical white matter fibers were grossly normal, suggesting that white matter disorganization is largely limited to cortico-cortical fibers, even though brainstem and cerebellar anomalies have been reported with conventional imaging [4]. While the absence of most tracts was determined by DTI tractography, the absence of the arcuate fasciculus was seen both with tractography and by the lack of normal architecture on DTI color images. The left arcuate fasciculus is thought to connect regions of the brain associated with receptive and expressive language [21]. Given that speech is severely affected in Aicardi subjects in general [3] and in these two subjects specifically, the absence of the left arcuate might constitute at least one neurological basis for their clinical speech deficit. The lack of other cortico-cortical tracts may prove to be clinically significant, though data on the neurocognitive correlates of these tracts are not well established. A larger number of individuals with Aicardi syndrome would have to be imaged to establish a link between presence or absence of tracts and cognitive outcome.

Individuals with both callosal agenesis and associated cortical malformations, with similar DTI acquisitions to the subjects with Aicardi syndrome, demonstrated grossly normal cortical and subcortical connectivity. These results suggest that the absence of these tracts in Aicardi subjects is not due to technical limitations of DTI acquisition and tractography procedures, but is instead a result of underlying anatomical abnormalities in these subjects. Furthermore, the absence of multiple major cortico-cortical association white matter tracts appears to be specific to Aicardi syndrome, and not a common feature of individuals with cortical malformations and callosal dysgenesis.

Since DTI findings can only be definitively verified by histological analysis, DTI and autopsy findings should be examined in conjunction. Several previous postmortem studies have been performed on Aicardi subjects [22-26]. Although these studies otherwise report grossly normal white matter structure and myelination, none perform histologic tract tracing, which would be necessary to determine the presence and abundance of individual white matter tracts. To our knowledge this is the first examination of Aicardi syndrome using DTI.

Although our results suggest gross deficits in white matter organization of Aicardi subjects, caution should be used in generalizing them. Given the degree of anatomic diversity already seen in Aicardi subjects [4], a larger cohort would be necessary to fully characterize the white matter organization of Aicardi syndrome. Considering that both of our subjects were nonverbal and demonstrated an absence of the left arcuate fasciculus, it would be particularly valuable to image patients with Aicardi syndrome who are able to speak. Since the causative gene(s) of Aicardi are still unknown, a fuller understanding of white matter organization could yield insight into the developmental mechanisms underlying the condition, and may thus be suggestive of candidate genes that are implicated in Aicardi syndrome. Once the connection between white matter organization and the behavioral characteristics of individuals with Aicardi is more fully understood, DTI imaging may prove to be a valuable prognostic tool for children born with the syndrome.

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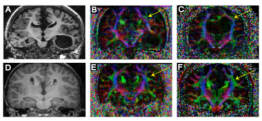

Fig 1.

T1-weighted and DTI images of Aicardi subjects and acallosal control subjects. T1-weighted coronal images are shown for subject 1 (A) and matched control subject (D). Coronal DTI colormaps are also shown for subject 1 (B), subject 2 (C), and their matched controls (E, F respectively). Yellow arrows indicate expected location of superior longitudinal fasciculus, normally visible as green longitudinal fibers. The superior longitudinal fasciculus is greatly diminished or absent in Aicardi subjects, while grossly intact in acallosal controls. Fiber orientation on DTI colormaps is encoded as: anterior-posterior, green; superior-inferior, blue; left-right, red.

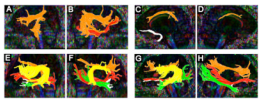

Fig 2.

Cortico-cortical connectivity of Aicardi subjects and acallosal controls. DTI tractography shows bilateral Probst bundles and right inferior fronto-occipital fasciculus (IFO) for subject 1 (A, right; B, left) and bilateral cingulum bundles and left uncinate fasciculus for subject 2 (C, right; D, left). Matched acallosal controls demonstrate all major cortico-cortical tracts (E-H), with the exception of the right arcuate fasciculus in the control matched for subject 2 (H). Tracts are colored as follows: cingulum bundle or probst bundle (orange), inferior fronto-occipital fasciculus (red), uncinate fasciculus (white), inferior longitudinal fasciculus (green), arcuate fasciculus (yellow).

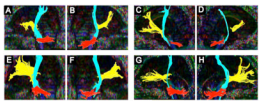

Fig 3.

Subcortical connectivity of Aicardi subjects and acallosal controls. DTI tractography reveals grossly intact anterior thalamic radiations (yellow), corticospinal tracts (blue), and middle cerebellar peduncles (red) in both Aicardi subjects (A-D) and acallosal controls (E-H). Images are lettered as in Fig 2.