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Abnormal Language Pathway in Children with Angelman Syndrome

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Abstract

Angelman Syndrome is a genetic disorder characterized by pervasive developmental disability with failure to develop speech. We examined the basis for severe language delay in Angelman Syndrome patients using diffusion tensor imaging. Magnetic Resonance Imaging/diffusion tensor imaging was performed in seven genetically confirmed Angelman Syndrome children (age:70±26 months, five males) and four age-matched controls to investigate the microstructural integrity of arcuate fasciculus and other major association tracts. Six of seven Angelman Syndrome children had unidentifiable left arcuate fasciculus while all controls had identifiable arcuate fasciculus. The right arcuate fasciculus was absent in six of seven Angelman Syndrome children and one of four controls. Diffusion tensor imaging color map suggested aberrant morphology of the arcuate fasciculus region. Other association tracts, including uncinate fasciculus, inferior-fronto-occipital fasciculus, inferior-longitudinal fasciculus, and corticospinal tract, were identifiable but showed decreased fractional anisotropy in Angelman Syndrome children. Increased apparent diffusion coefficient was seen in all tracts except uncinate fasciculus when compared to controls. Angelman Syndrome patients have global impairment of white matter integrity in association tracts, particularly, the arcuate fasciculus which shows severe morphological changes. This could be due to a potential problem with axon guidance during brain development possibly due to loss of UBE3A gene expression.

Keywords

Angelman Syndrome; Arcuate Fasciculus; Diffusion Tensor Imaging; Neuroimaging

Introduction

Angelman syndrome is a neurodevelopmental disorder associated with genetic abnormalities in the 15q11–13 region of the human genome. The abnormality is localized to the UBE3A gene. Clinical features of Angelman Syndrome include severe mental retardation, gait

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ataxia, and behavioral problems[1]. Seizures, microcephaly, and autistic features are often present[2]. A prevalent clinical feature of Angelman Syndrome is the absence of language and speech modalities[3].

The arcuate fasciculus is a white matter pathway that involves reciprocal connections between inferior frontal, parietal, and posterior temporal cortices, including the classical language regions, Broca's and Wernicke's area. Although it has not been possible to isolate specific white matter pathways with conventional MRI, the advent of MR diffusion tensor imaging has made it possible to isolate and quantify microstructural characteristics of specific white matter pathways in the brain. Diffusion tensor imaging assesses the diffusion pattern of water molecules in order to provide information about white matter tracts and/or tissue architecture. These scans are then analyzed using fiber tractography, which allows for the definition of specific white matter tracts[4]. The degree of restriction of water diffusion is quantified as apparent diffusion coefficient, and the directionality of water diffusion is presented as fractional anisotropy [5].

We recently published a study using diffusion tensor imaging to evaluate the integrity of cortical association tracts, including the arcuate fasciculus, in children with idiopathic global developmental delay [6]. While the arcuate fasciculus was unidentifiable on the left side in 11 of 20 subjects in the developmental delay group (bilaterally absent in 9 of 20), the tract was identifiable, bilaterally, in all typically developing controls. Given this finding, and the fact that children with Angelman Syndrome demonstrate severe language impairment, we hypothesized that the arcuate fasciculus would be unidentifiable or malformed in Angelman Syndrome children when tractography methods were applied. To further characterize fiber distribution in the arcuate fasciculus region, we also utilized a standardized region-of-interest (ROI) approach to examine the ratio of fibers projecting bidirectionally in the anterior/posterior direction to those projecting in the medial/lateral direction. We hypothesized that Angelman Syndrome children would show a lower overall ratio of fibers in the arcuate fasciculus region, with this difference primarily being driven by a lack of anterior/posterior fibers.

Study Design and Methods

Participants

Seven Angelman Syndrome children (age: 70 ± 26 months, five males) and four age-matched normal controls (age: 79.8 ± 17 months, four males) were studied. Control participants had measured intellectual functioning within one standard deviation of the normative mean, and none had current or historical medical or psychiatric diagnoses. Angelman Syndrome children underwent fluorescent in situ hybridization or methylation testing to confirm diagnosis. In the Angelman Syndrome group, five children had deletions in the 15q11–13 genomic region. One subject had confirmed uniparental paternal disomy and one presented with abnormal SNRPN methylation testing, but additional information regarding the specific genetic lesion was not available. Imaging data on all subjects was obtained through either a routine clinical scan or as part of an approved research protocol after recruitment. Five of seven Angelman Syndrome children were recruited and written informed consent was obtained from legal guardians. Data from two out of seven Angelman Syndrome children were obtained clinically. The Human Investigations Committee of Wayne State University granted permission for the retrieval and analysis of archival clinical data. The study has been approved by the Institutional Review Board at Wayne State University.

Neuropsychological Evaluation

Five of seven Angelman Syndrome children completed developmental evaluations assessing global cognitive functioning, fine motor skills, language functioning, parent ratings of adaptive behavior and behavioral problems. The developmental characteristics of the Angelman Syndrome children are presented in Table 1. As can be seen, the children in this sample are measured in the moderate-severely impaired range across domains with a mean adaptive behavior composite measured in the low range, more than two standard deviations below the normative mean.

Imaging Protocol and Fiber Tracking

Axial-diffusion tensor imaging array spatial sensitivity encoding technique data were acquired on a 3T GE Signa scanner (GE Healthcare, Milwaukee, WI) at TR =1250 ms, TI =88.7 ms, field of view =240 cm, 128x128 matrix, contiguous 3 mm thickness slices to cover the whole brain using 55 isotropic gradient directions with $b = 1000 \text{ s/mm}^2$, one $b = 0$ acquisition, and number of excitations (NEX =1) for a total acquisition time of 12 minutes. A 3-D fast spoiled gradient-echo image was also acquired from whole brain using TR/TE/TI of 9.12/3.66/400 ms, slice thickness of 1.2 mm, and planar resolution of $0.9375 \times 0.9375 \text{ mm}^2$. The fast spoiled gradient-echo image was used as anatomical reference for this study.

Double refocusing pulse was used to reduce eddy-current artifacts. In addition, array spatial sensitivity encoding technique was performed to further reduce geometric distortion because of the sequence design.

All of the children with Angelman Syndrome were sedated for the scan and monitored for the duration by a trained sedation nurse. None of the 4 control children were sedated for the scan. After acquisition, all datasets were assessed for quality and deemed acceptable for analysis. No scans were repeated due to movement or other artifacts.

Tensor calculation and tractography were performed using DTI-Studio software [October 2007 version 2.401][7]. Tractography was carried out based on the Fiber Assignment by Continuous Tracking algorithm[7] with fiber propagation starting at an fractional anisotropy threshold value of >0.2 . The fiber propagation was stopped at a fractional anisotropy threshold <0.2 or angle threshold >60 degrees.

The tracking protocol followed to isolate the arcuate fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, and the inferior-longitudinal fasciculus was described previously [6]. In this study, we did not attempt to track the cingulate fasciculus and we did track the corticospinal tract. To identify the corticospinal tract, an ROI was placed at the level of the cerebral peduncles using an “OR” operator in the axial slice. The second ROI was drawn using an “AND” operator in the posterior limb of the internal capsule on the axial slice[8,9]. The third ROI was placed at the level of the primary motor cortex in the axial plane. All fractional anisotropy and apparent diffusion coefficient metrics for each fiber tract were calculated with DTI-studio software by two independent observers. Inter-rater reliability was calculated by $2 \times (R2 - R1) / (R2 + R1)$ (R =Rater ROI measure) and percent difference averaged for individual tracts. There was less than 5% difference between raters for fractional anisotropy and apparent diffusion coefficient of each tract. An average between raters measurement was taken for each tract and used for group statistics.

Color Map Quantification

The direction of individual fibers in diffusion tensor imaging data can be imaged by color-encoded anisotropy maps, where three components of the eigenvector v_1 , in association with the largest eigenvalue, are color coded using an RGB-color model which is

symmetrical with respect to all color axes. The color axes are aligned with the patient coordinate system (green: anterior-to-posterior, red: medial-to-lateral, blue: superior-to-inferior). As a direct metric to quantify a measure of fiber directionality we measured anterior-posterior components (green signal of color coded map) and medial-lateral (red signal of color coded map) in the region of arcuate fasciculus.

To analyze the arcuate fasciculus region of the color map, we developed a standardized region of interest approach utilizing the Statistical Parametric Mapping deformation toolbox (<http://www.fil.ion.ucl.ac.uk/spm>). We chose to use this standardized approach to reduce the inter-rater variability that is often introduced when manually defining ROI's. To start, a single ROI covering the entire pre- and post-central white matter projections in the left hemisphere was manually delineated in common Montreal Neurological Institute space. For each subject, we then estimated the spatial deformation field to normalize the coordinates of the subject's fractional anisotropy image to the Montreal Neurological Institute fractional anisotropy template. We used our own pediatric Montreal Neurological Institute fractional anisotropy template as a target image for ROI definition and spatial normalization in order to minimize estimation errors due to the mismatch of head size, shape, and white matter distribution between children and adults. The fractional anisotropy template was generated from the fractional anisotropy images of 37 normal children using Statistical Parametric Mapping DARTEL toolbox which has been widely utilized to generate the Montreal Neurological Institute template using a series of specific group data[10]. Information pertaining to how each subject's image was altered to match this common space (i.e. stretching, rotation etc.) was stored in the transformation matrix.

To map our previously defined ROI back to a subject's individual head space, an inverse of the transformation was applied to the common ROI to generate an individual ROI for every subject. Each subject's ROI was then placed on their respective diffusion tensor imaging color map. The red and green signal intensities for the region were obtained using the DTIStudio software. A green/red ratio was then calculated for all cases and controls. Given that the colors in the map represent the direction in which the white matter fibers travel, we defined this green/red ratio as the anterior-posterior/medial-lateral ratio.

Statistical Analysis

First, descriptive statistics were conducted for fractional anisotropy and apparent diffusion coefficient for each tract by group (Table 2). Next, to determine whether Angelman Syndrome children significantly differed from control children on microstructural integrity of uncinate fasciculus, inferior-longitudinal fasciculus, inferior fronto-occipital fasciculus, and corticospinal tract, separate 2 (Group: Angelman Syndrome vs. control) x 2 (Side: left vs. right) repeated measures ANCOVAs, controlling for age, were conducted with both fractional anisotropy and apparent diffusion coefficient for each of the tracts serving as dependent variables. Follow-up tests were conducted to explore significant interactions. Finally, to determine whether anterior-posterior/medial-lateral ratios differed between Angelman Syndrome and control children, an independent t-test was conducted. Absolute anterior-posterior and medial-lateral values were also compared using MANCOVA, controlling for age, to determine which values were driving the difference in the anterior-posterior/medial-lateral ratio. Within-group (Angelman Syndrome group) Pearson correlations were used to examine associations between parent-reported Vineland Adaptive Behavior domain scores and diffusion tensor imaging metrics.

Results

Tract Differences

Arcuate Fasciculus—The arcuate fasciculus fiber tract could not be identified in six of seven Angelman Syndrome children in the left hemisphere while all control children showed an identifiable arcuate fasciculus (Figure 1). In the right hemisphere, the arcuate fasciculus fiber tract could not be identified in six of seven Angelman Syndrome children and one of four controls. The arcuate fasciculus fibers identified in our Angelman Syndrome sample were found in two different children. Fractional anisotropy and apparent diffusion coefficient values for the arcuate fasciculus were not compared due to the lack of an identifiable tract in the Angelman Syndrome children.

Other Association Tracts—For uncinate fasciculus, results revealed a significant group effect for fractional anisotropy ($F(1,8) = 54.15, p < .001$) with Angelman Syndrome children having lower fractional anisotropy than control children. For apparent diffusion coefficient of the uncinate fasciculus, no significant differences emerged between the groups. For inferior-longitudinal fasciculus, results revealed a significant group effect for both fractional anisotropy ($F(1,8) = 24.08, p = .001$) and apparent diffusion coefficient ($F(1,8) = 9.20, p = .016$); Angelman Syndrome children had significantly lower fractional anisotropy and higher apparent diffusion coefficient than control children. For inferior fronto-occipital fasciculus, there were also significant group effects for both fractional anisotropy ($F(1,7) = 83.78, p < .001$) and apparent diffusion coefficient ($F(1,7) = 10.85, p = .013$), such that Angelman Syndrome children had significantly lower fractional anisotropy and higher apparent diffusion coefficient than control children. Finally, for corticospinal tract, results revealed a significant group effect for fractional anisotropy ($F(1,8) = 9.43, p = .015$), with Angelman Syndrome children having significantly lower fractional anisotropy than control children, and a significant group by side interaction for apparent diffusion coefficient ($F(1,8) = 7.45, p = .026$). Follow-up tests indicated that control children showed no differences in apparent diffusion coefficient between the left and right corticospinal tract, while Angelman Syndrome children showed a trend towards having significantly higher apparent diffusion coefficient in the left corticospinal tract than in the right ($F(1,11) = 4.37, p = .061$). Correlations between diffusion tensor imaging metrics and Vineland Adaptive Behavior domains were also examined; none of the correlations reached significance.

Anterior-Posterior/Medial-Lateral Ratio Differences

Results of the independent t-test revealed that Angelman Syndrome children had significantly lower anterior-posterior/medial-lateral ratios than control children ($t(9) = 3.99, p = .003$ (Figure 2). The MANCOVA revealed a significant overall model ($F(1,10) = 9.94, p = .006$). Follow-up ANCOVAs indicated that the groups significantly differed on anterior-posterior values ($F(1,10) = 27.91, p = .001$), such that the Angelman Syndrome group had lower values than the control group. The groups did not differ on medial-lateral values.

Discussion

Here we present novel findings of applying diffusion tensor imaging tractography to study brain connectivity in Angelman Syndrome. A major finding is that the arcuate fasciculus in the left hemisphere could not be identified in six of seven Angelman Syndrome children while all four control children showed identifiable arcuate fasciculus in the left hemisphere. The seventh Angelman Syndrome subject had a partially identifiable arcuate fasciculus. In the right hemisphere, the arcuate fasciculus fiber tract was absent in six out of seven Angelman Syndrome children and one out of four control children. Grossly abnormal arcuate fasciculus tracts as identified via deterministic tractography were further

corroborated by a non-tractographic approach that demonstrated that the arcuate fasciculus region in Angelman Syndrome children has a significantly lower ratio of anterior-posterior fibers to medial-lateral fibers when compared to controls. After further exploration, we found that the difference in this ratio was being driven by the lack of anterior-posterior fibers in the arcuate fasciculus region.

Examination of the other association tracts revealed that Angelman Syndrome children had significantly lower fractional anisotropy values in all association tracts when compared to the normal control group. Furthermore, apparent diffusion coefficient values were significantly higher in inferior-longitudinal fasciculus and inferior fronto-occipital fasciculus in Angelman Syndrome children compared to controls. The corticospinal tract also showed increased apparent diffusion coefficient in Angelman Syndrome children with L>R asymmetry as compared to controls.

The arcuate fasciculus is a white matter tract which connects the language comprehension region of the temporal lobe with the speech generating region of the frontal lobe. Evidence suggests this tract is involved in language [11] and higher cognitive functions [12]. Studies examining the relationship between speech and language lateralization have primarily implicated the left hemisphere as the more dominant hemisphere[13]. More recently, diffusion tensor imaging studies of the arcuate fasciculus have also supported such anatomical laterality[14]. In this study, a finding of unidentifiable arcuate fasciculus in the right hemisphere is not necessarily surprising given that our own studies[6] have shown increased likelihood that the arcuate fasciculus is bilaterally unidentifiable in children with global developmental delay and that other studies have shown that the right arcuate fasciculus can be unidentifiable in healthy controls[15]. However, a finding showing abnormalities in the left arcuate fasciculus is important given the potential relationship it shows to speech and language functions. Yet, because children with Angelman Syndrome also present with profound mental impairment, it is still unclear if the present findings in arcuate fasciculus are related more to the impairment of language or to the overall global cognitive deficit seen in Angelman Syndrome children, or both.

Arcuate fasciculus unidentifiability could either be due to regional abnormalities in white matter architecture or abnormal development of the pathway. Since tracking a pathway depends on fractional anisotropy thresholds, a track may be unidentifiable if fractional anisotropy values along a pathway go below the threshold as a result of local microstructural factors such as poor myelination or abnormal fiber crossing. The fractional anisotropy threshold used in the present study was 0.2 and the fractional anisotropy values of the major association tracts are above 0.4 (Table 2). Similarly, estimates of fractional anisotropy for the anterior-posterior/medial-lateral measurement (fibers in the vicinity of where the arcuate fasciculus should be) were also above threshold (Table 2), indicating that a low fractional anisotropy threshold is not responsible for the findings.

The significantly lower anterior-posterior/medial-lateral ratio in Angelman Syndrome children suggests that regional disorganization of fiber bundles in arcuate fasciculus region could be an important mechanism behind the unidentifiability of arcuate fasciculus. This may support that arcuate is unidentifiable as more a result of the disruption of early developmental processes due a germ line mutation of UBE3A which had an effect on overall white matter development, particularly in the region of arcuate.

There are several genetic mechanisms related to Angelman Syndrome: de novo deletions of maternal 15q11–13, uniparental paternal disomy of 15q11–13, imprinting defect or mutation of the UBE3A gene[16]. Each of these mechanisms includes a loss in expression of the UBE3A gene. UBE3A is principally expressed in the neurons of the hippocampus,

cerebellum and cortex [17] and is involved in the ubiquitin proteasome system which is the primary mechanism by which protein degradation is regulated inside the cell. Degradation of proteins through ubiquitination during development is a common mechanism for regulating levels of axon guidance molecules[18,19]. Evidence from genetic studies looking at the development of several other fiber tracts, including corticospinal tract[20], midbrain dopaminergic axons[21], and sensory axons[22], indicate that axon guidance mechanisms play an important role in the proper formation of these tracts. This could also mean that alterations in the mechanisms responsible for regulating axon guidance in part affect the development of the arcuate fasciculus, particularly the orientation of its fibers. Subsequently, this may manifest as abnormal tracts at macroscopic levels noted in the study. It is well known that developing axon growth cones compete with each other for the limited amount of axon guidance molecules and poor development of one pathway may result in crowding by other pathways[23]. Such crowding out of the arcuate fasciculus by other tracts could explain the findings of low anterior-posterior/medial-lateral ratio and unidentifiable arcuate fasciculus in children with Angelman Syndrome.

Similarly, diffusion tensor imaging study of $Fz3^{-/-}$ knockout mice show an absence or severe reduction in the size of major tracts in the developing forebrain and a failure of sensory axons in the spinal cord to grow rostrally after crossing the midline[24]. Thus, while our current knowledge about arcuate fasciculus development is rudimentary, future mechanistic studies evaluating genetic control of arcuate fasciculus development may shed light on this issue.

An analysis of the other association tracts also suggests a global underdevelopment of white matter and fit well with previous findings suggesting abnormal myelin development in children with Angelman Syndrome[25]. We found an overall decrease in fractional anisotropy in all association tracts and increase in apparent diffusion coefficient in inferior-longitudinal fasciculus, inferior fronto-occipital fasciculus, and corticospinal tract in Angelman Syndrome children compared to control children.

In addition, the Angelman Syndrome children showed more severe imaging abnormalities and had poorer functioning across major developmental domains (moderate-severely impaired versus mildly impaired) in each of the domains than the developmentally delayed children in Sundaram et al., 2008. All the five association tracts studied in Angelman Syndrome children significantly differed from controls compared to the developmentally delayed children who, as a group, differed from controls only in the arcuate and inferior longitudinal fasciculi. Despite the clinical similarities between the two groups, it is not surprising that the Angelman children presented with more severe white matter abnormalities given that they had more severe developmental impairment. These findings may also be related to the genetic abnormalities discussed above.

Limitations

This study is not without limitations. The ROI fiber tracking approach, while increasing the accuracy of measurements of apparent diffusion coefficient and fractional anisotropy for the tracts being studied, could potentially be less reproducible. However, to address this issue we used a blinded two-rater approach and a multiple region analysis with an inter-rater variability threshold <10%. In addition, adequately standardized and previously published protocols using minimum number of ROIs (usually two ROIs with a maximum of three ROIs for each tract) were used by both raters, thus improving the reproducibility of the results. Both raters were agreeable within the range of the threshold for all tracts. In addition, it has to be noted that reproducibility is not an issue when examining a tract that is not identifiable (i.e., the arcuate fasciculus).

Furthermore, the tractography method has an inherent weakness when it comes to segregating specific fiber tracts near locations where fiber tracts cross. At distinct points in the brain where fiber tracts converge and run together, using the current methods, it becomes difficult to distinguish one tract from another. To reduce the error associated with this problem, we chose to use a standardized protocol that incorporated specific landmarks known to punctuate each individual tract we analyzed. In doing so, we limited the degree to which crossing fibers would be included in the analysis.

Conclusion

To our knowledge this is the first study to use the diffusion tensor imaging tractography method to examine white matter pathways in children with Angelman Syndrome. We present evidence to suggest an underdeveloped arcuate fasciculus fiber as well as changes in apparent diffusion coefficient and fractional anisotropy metric values in other major tracts. In addition, analysis of the arcuate fasciculus on the diffusion tensor imaging color map suggests aberrant directionality of axons in the region. These findings could be related to the effect that genetic abnormalities have on axon guidance and development in children with Angelman Syndrome.

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Figure 1. Color map and diffusion tensor imaging tractography of the arcuate fasciculus on the left side in an Angelman Syndrome subject (A) and a control subject. The white arrow indicates the arcuate fasciculus region.

Figure 2.
Anterior-posterior/medial-lateral ratios of Angelman Syndrome children and control children

Table 1

Demographic and adaptive behavior domain scores for Angelman Syndrome participants

Subject #	Age (in months)	Gender	Communication [†]	Daily Living Skills [†]	Socialization [†]	Motor Skills [†]	Adaptive Behavior Composite [†]
1	49	M	49	55	59	54	52
2	59	F	61	58	72	56	59
5	105	M	54	57	62	N/A	58
6	57	M	74	83	77	67	72
11	71	M	44	40	59	51	46
4	106	F					
10	43	M					
Mean (SD)			70.00 (25.78)	56.40 (11.67)	58.00 (15.47)	67.00 (7.97)	57.00 (6.98)
							57.40 (9.69)

† Scores are reported as Standard Scores (Mean=100, SD=15)

Table 2

Mean and standard deviation of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values for the four other association tracts: uncinate fasciculus(UF), inferior-longitudinal fasciculus(ILF), inferior fronto-occipital fasciculus(IFO), and corticospinal (CST). Additionally, the fractional anisotropy value for the ROI used to calculate the anterior-posterior/medial-lateral (A-P/M-L) ratio is displayed.

Tract	Mean FA $\pm$ SD			Mean ADC $\pm$ SD		
	Normal	AS	p-value	Normal	AS	p-value
Left UF	.4574 $\pm$.03129	.3888 $\pm$.02221	<.001	.0025500 $\pm$.00010000	.0027000 $\pm$.00015000	0.172
Right UF	.4657 $\pm$.01412	.4213 $\pm$.01671		.0025625 $\pm$.00011087	.0026714 $\pm$.00016797	
Left ILF	.5343 $\pm$.03863	.4357 $\pm$.02179	0.001	.0025875 $\pm$.00015478	.0028071 $\pm$.00011701	0.016
Right ILF	.5466 $\pm$.03973	.4502 $\pm$.02693		.0025625 $\pm$.00014930	.0028000 $\pm$.00012910	
Left IFO	.5310 $\pm$.03383	.4468 $\pm$.01560	<.001	.0025250 $\pm$.00011902	.0027214 $\pm$.00010351	0.013
Right IFO[£]	.5396 $\pm$.01329	.4680 $\pm$.02044		.0025000 $\pm$.00008165	.0027083 $\pm$.00014634	
Left CST	.6411 $\pm$.03706	.5780 $\pm$.03009	0.015	.0022750 $\pm$.00009574	.0024071 $\pm$.00008381	.026 [†]
Right CST	.6420 $\pm$.03590	.5753 $\pm$.03008		.0023000 $\pm$.00012247	.0023357 $\pm$.00005563	
A-P/M-L ROI FA	0.3689 $\pm$.02568	0.2534 $\pm$.03211				

[†] Group x side interaction

[£] Calculated with 6 Angelman Syndrome and 4 Controls