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Clinical Observations

Frontal Aslant Tract Abnormality on Diffusion Tensor Imaging in an Aphasic Patient With 49, XXXXY Syndrome

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ABSTRACT

BACKGROUND: The karyotype 49, XXXXY is one of the most severe forms of chromosome aneuploidy and is characterized clinically by developmental delay and profound language impairment, particularly involving expressive language functions. We describe the neurocognitive profile and structural anatomy of language pathway in a 2-year-old boy with 49, XXXXY syndrome with expressive aphasia. **METHODS:** Retrospective chart review of the patient was performed. We characterized the language deficits using neuropsychologic testing. We further studied the language pathways using diffusion tensor imaging analytical technique. **RESULTS:** The neurocognitive profile of the patient showed relative weakness of expressive language skills compared with other domains. Diffusion tensor imaging analysis demonstrated a poorly developed frontal aslant tract, a weak indirect segment of arcuate fasciculus, and normally developed direct segment of arcuate fasciculus. The frontal aslant tract is a novel pathway that connects the Broca's area with the anterior cingulate and presupplementary motor area and plays a role in the "motor stream" of language. **CONCLUSION:** A poorly developed frontal aslant tract may underlie the expressive language deficits and provide some insight into the role of X chromosome in modulating the development of language tracts.

Keywords: 49, XXXXY, chromosome aneuploidy, arcuate fasciculus, language

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Introduction

The incidence of sex chromosome aneuploidy is approximately 1 in 400 live births.[1] Among these, 49, XXXXY is one of the most severe and rare forms of sex chromosome aneuploidy with an incidence of approximately 1 in 85,000 live male births.[2] Previous case series of these patients have reported severe developmental delay, defects in skeletal development, and cardiac and genital abnormalities.[3] Children with 49, XXXXY are often found to have severe neurocognitive deficits, global intellectual disability, and profound language deficits.[4] In this report, we characterize the neurocognitive functions in a child with 49, XXXXY chromosome aneuploidy and evaluate the language pathway morphology using diffusion tensor imaging (DTI). We further review the literature about brain morphologic abnormalities in patients with 49, XXXXY syndrome and the role of X chromosome in language development.

Patient Description

A 2-year-old Caucasian boy with genetically proven 49, XXXXY chromosome abnormality presented to the clinic with developmental delay, particularly involving language functions. He was born at term

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after an uncomplicated pregnancy. He was diagnosed at birth by karyotyping due to dysmorphic features, cardiac defects, and undescended testes. On examination, he had normal head circumference and normal stature. He had dysmorphic features, including hypertelorism, epicanthal folds, malar hypoplasia, and mild retrognathia. He made good eye contact and had a pleasant affect. Language assessment showed impairment of expressive speech with ability to speak only two words. However, he was able to follow simple one-step commands and pointed to a few body parts. The remainder of the neurological examination was within normal limits.

Neuropsychologic testing at 3 years and 9 months was performed. It included direct assessment of cognitive and language functions, and semistructured interview of adaptive behavioral functioning, including assessment of communication, daily living, socialization, and motor skills. The findings are presented in the Table. As can be seen in the table, functioning across most domains was measured in the moderately low or low average ranges. Statistically significant normative and relative weaknesses were noted in expressive language skills. Results of assessment of autism spectrum symptoms using semistructured interview and direct observation were subthreshold for a diagnosis on the autism spectrum.

Magnetic resonance imaging (MRI) of the brain without contrast demonstrated multiple T2 hyperintensities in the white matter in frontal-parietal regions bilaterally, predominantly in the periventricular areas and centrum semiovale. In addition, brain MRI also showed multiple areas of increased susceptibility in the cerebellar hemispheres bilaterally.

This MRI study utilized a novel DTI analytical technique providing high-resolution tracking of individual branches of the arcuate fasciculus. This method, called "diffusion weighted image-based maximum *a posteriori* probability (DWI-MAP) classifier,"[5] automatically detects four separate language branches, which connect four distinctive language areas including the Broca's area for speech, Wernicke's area for comprehension, inferior parietal area for reading, and premotor area for fluency.[6] Briefly, whole-brain tractography using independent component analysis with the ball and stick model (independent component analysis + ball and stick model) was performed to isolate up to three fiber bundles crossing at every voxel.[7] The resulting streamline tractography was sorted using the diffusion weighted image-based maximum *a posteriori* probability classifier to identify the four language branches in both hemispheres: C_1: Broca's area to premotor area, C_2: Broca's area to Wernicke's area, C_3: premotor to inferior parietal area, and C_4: inferior parietal area-Wernicke's area. This analysis found poorly developed branches of the language pathway in C_1: frontal aslant tract (effect size of streamline volume, patient volume−mean volume of five controls/standard deviation volume of five controls = 6.12) and C_3: indirect segment of arcuate fasciculus of both hemispheres (effect size = 3.74) compared with age- and gender-matched healthy control (Figure). In contrast, the direct segment of arcuate fasciculus (C_2) and the fibers in Wernicke's area (C_4) were intact but showed slightly weaker connection compared with age- and gender-matched healthy control (effect size < 1.20). The frontal aslant tract of the right hemisphere may not be reorganized because it is also poorly developed compared with the matched healthy control.

TABLE.
Results of Cognitive and Adaptive Behavior Testing

Domain	Scaled Score	Range
Cognitive testing[*]		
Block design	6	Low average
Object assembly	7	Low average
Information	5	Borderline
Receptive vocabulary	9	Average
Expressive vocabulary	1	Extremely low
Adaptive behavior[†]		
Receptive language	12	Moderately low
Expressive language	6	Low
Personal skills	11	Moderately low
Domestic skills	14	Adequate
Community skills	10	Moderately low
Interpersonal relationships	10	Moderately low
Play and leisure time	11	Moderately low
Coping skills	9	Low
Gross motor skills	11	Moderately low
Fine motor skills	10	Moderately low

Shaded areas = normative and relative weaknesses.
[*] Mean = 10, SD = 3.
[†] Mean = 15, SD = 3.

Discussion

We describe, for the first time, the microstructural abnormality in a child with 49, XXXXY syndrome to account for the impaired expressive but relatively spared receptive language functions.

The 49, XXXXY syndrome was first described by Fraccaro et al.[8] and the most common developmental impairments in these patients are severe dyspraxia in both oral and verbal domains. In fact, the majority of children with 49, XXXXY have relatively intact nonverbal and also receptive vocabulary and comprehension skills.[9] Neurological examination and neuropsychologic testing in our patient was consistent with this neurocognitive profile.

The role of different segments of the arcuate fasciculus in language has been elucidated using tractography. A novel language tract called the frontal aslant tract has been described, which is a direct pathway connecting the Broca region with the anterior cingulate and presupplementary motor area.[10] This tract is left lateralized in right-handed subjects, suggesting a possible role in language function. This role has been corroborated with intraoperative electrical stimulation of the left frontal aslant tract resulting in speech arrest suggesting that the frontal aslant tract forms a part of the motor stream that plays an important role in speech production.[11,12] The DTI findings in our patient showed a poorly developed frontal aslant tract (connecting the Broca area to premotor cortex) and a weak indirect segment of the arcuate fasciculus (connecting the Broca area to the inferior parietal cortex). These findings may indicate the neural substrate for the oral dyspraxia in this patient and potentially for the prevalence of this impairment in children with 49, XXXXY. However, studies on a larger number of patients with this disorder are needed to validate this clinically relevant structure−function association.

In a series of 19 patients with 49, XXXXY syndrome, brain MRI identified T2 hyperintensities in white matter and thinning of the corpus callosum.[13] These findings suggested that the X chromosome likely plays a role in the structural development of white matter tracts. Studies examining the effects of increased dosage of sex chromosomes on language development in patients with X/Y aneuploidies found that supernumerary X chromosomes are associated with impairments in language structure compared with pragmatic language.[14] Another study suggested that in cases of a supernumerary X, slow rates of prenatal neuronal growth selectively retard the development of the left hemisphere, thereby disturbing the normal process of hemispheric lateralization, specifically the specialization of the left cerebral hemisphere for language functions, thus contributing to expressive language deficits.[15] These studies along with our finding of poor development of the frontal aslant