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

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Abstract

Background—49, XXXXY is one of the most severe forms of chromosome aneuploidy and is characterized 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 neuropsychological testing. We further studied the language pathways using diffusion tensor imaging (DTI) analytical technique.

Results—Neurocognitive profile of the patient showed relative weakness of expressive language skills compared to other domains. DTI analysis demonstrated a poorly developed frontal aslant tract; a weak indirect segment of arcuate fasciculus and normally developed direct segment of arcuate fasciculus. Frontal aslant tract is a novel pathway, which connects Broca's area with the anterior cingulate and pre-supplementary motor area and plays a role in the 'motor stream' of language.

Conclusion—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 births¹. 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 births². Previous case series of these patients have reported severe developmental delay, defects in skeletal development, cardiac and, genital abnormalities³. Children with 49, XXXXY are often found to have severe neurocognitive deficits, global intellectual disability and profound language deficits⁴. 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 morphological abnormalities in patients with 49, XXXXY syndrome and the role of X chromosome in language development.

Case Report

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 full term after an uncomplicated pregnancy. He was diagnosed at birth by karyotyping due to dysmorphic features, cardiac defects and undescended testes. On exam 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 exam was within normal limits.

Neuropsychological testing at 3 years and 9 months was performed. It included direct assessment of cognitive and language functions, and semi-structured interview of adaptive behavioral functioning including assessment of communication, daily living, socialization, and motor skills. The findings are presented in Table 1. As can be seen in the table, functioning across most domains was measured in the moderately low/low average ranges. Statistically significant normative and relative weaknesses were noted in expressive language skills. Assessment of autism spectrum symptoms using semi-structured interview and direct observation, were subthreshold for a diagnosis on the autism spectrum.

Magnetic resonance imaging (MRI) 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, MRI brain 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”⁶, automatically detects four separate language branches which connect four distinctive language areas including Broca’s area for speech, Wernicke’s area for comprehension, inferior parietal area

for reading, and premotor area for fluency⁷. Briefly whole brain tractography using independent component analysis with ball and stick model was performed to isolate up to 3 fiber bundles crossing at every voxel (ICA+BSM)⁸. The resulting streamline tractography was sorted using the DWI-MAP classifier to identify the four language branches in both hemispheres: "C₁: Broca's area to premotor area", "C₂: Broca's area to Wernicke's area", "C₃: premotor to inferior parietal area" and "C₄: inferior parietal area-Wernicke's area". This analysis found poorly developed branches of the language pathway in C₁: frontal aslant tract, (effect size of streamline volume, |patient volume-mean volume of five controls|/standard deviation volume of five controls =6.12), and C₃: indirect segment of arcuate fasciculus of both hemispheres (effect size=3.74) compared with age-gender matched healthy control (figure 1). In contrast, the direct segment of arcuate fasciculus (C₂) and the fibers in Wernicke's area (C₄) were intact but showed slightly weaker connection compared with age and gender matched healthy control (effect size < 1.20). The frontal aslant tract of right hemisphere may not be reorganized since it is also poorly developed compared with the matched healthy control.

Discussion

Herein 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. and the most common developmental impairments in these patients are severe dyspraxia in both oral and verbal domains⁹. In fact, the majority of children with 49, XXXXY have relatively intact nonverbal and also receptive vocabulary and comprehension skills⁵. Neurological examination and neuropsychological 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. Recently, a novel language tract called the frontal aslant tract has been described which is a direct pathway connecting Broca's region with the anterior cingulate and pre-supplementary motor area¹⁰. 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 Broca's area to premotor cortex) and a weak indirect segment of arcuate fasciculus (connecting Broca's area to 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 49XXXXY. However, studies on a larger number of patients with this disorder are needed to validate this clinically relevant structure-function association.

In a case series of 19 patients with 49, XXXXY syndrome, MRI brain found T2 hyperintensities in white matter and thinning of the corpus callosum (CC)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 chromosome is associated with impairments in language structure as compared to pragmatic language¹⁴. 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 deficits¹⁵. These studies along with our finding of poor development of the frontal aslant pathway suggest the role of the X chromosome in the development of white matter tracts, particularly the frontal aslant segment of the arcuate fasciculus. This anatomical disruption may underlie the specific expressive language impairments often seen in patients with 49, XXXXY syndrome. In conclusion, the present case study illustrates that the X chromosome may play a role in the development of certain aspects of language via formation of specific language pathway segments.

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Figure 1.

Four language pathway segments obtained from DWI-MAP classifier ("C₁: Broca's area to premotor area", "C₂: Broca's area to Wernicke's area", "C₃: premotor to inferior parietal area", "C₄: Wernicke's area to inferior parietal area). Top: 49,XXXXY patient, Bottom: age-gender matched healthy control. For DWI-MAP classifier, whole brain tractography of individual subject was obtained using ICA+BSM tractography and sorted into four language pathways (C₁₋₄) by filtering whole brain tractography with spatially deforming standard clusters of semantic language areas such as Broca's area (BA 44/45), Wernicke's area (BA 22), premotor (BA 6), and parietal area (BA 39) which were obtained from twenty healthy

controls. Note the poor formation of C₁ (arrow) and weak C₃ in the left hemisphere of the patient with 49,XXXXY.

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Table 1

Results of cognitive and adaptive behavior testing

Domain	Scaled score	Range
<i>Cognitive Testing</i> [‡]		
Block Design	6	Low Average
Object Assembly	7	Low Average
Information	5	Borderline
Receptive vocabulary	9	Average
Expressive vocabulary	1	Extremely Low
<i>Adaptive Behavior</i> ^{‡‡}		
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 & leisure time	11	Moderately Low
Coping skills	9	Low
Gross Motor skills	11	Moderately Low
Fine motor skills	10	Moderately Low

[‡]=mean=10, SD=3^{‡‡}=mean=15, SD=3

shaded areas = normative and relative weaknesses