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Brain morphological abnormalities in 49,XXXXY syndrome: A pediatric magnetic resonance imaging study☆☆

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ABSTRACT

As a group, people with the sex chromosome aneuploidy 49,XXXXY have characteristic physical and cognitive/behavioral tendencies, although there is high individual variation. In this study we use magnetic resonance imaging (MRI) to examine brain morphometry in 14 youth with 49,XXXXY compared to 42 age-matched healthy controls. Total brain size was significantly smaller ($t = 9.0$, $p < .001$), and rates of brain abnormalities such as colpocephaly, plagiocephaly, periventricular cysts, and minor craniofacial abnormalities were significantly increased. White matter lesions were identified in 50% of subjects, supporting the inclusion of 49,XXXXY in the differential diagnosis of small multifocal white matter lesions. Further evidence of abnormal development of white matter was provided by the smaller cross sectional area of the corpus callosum. These results suggest that increased dosage of genes on the X chromosome has adverse effects on white matter development.

1. Introduction

Approximately 1 in 400 people are born with a sex chromosome combination other than XX or XY (Nielsen and Wohlert, 1990; Ratcliffe, 1994). Most sex chromosome variations (SCVs) are from the addition of a single X or Y (i.e., XXY, XXX, or XYY). However, more than one supernumerary chromosome may occur; in approximately 1 of 85,000 to 100,000 live male births, boys have 3 extra X chromosomes (49,XXXXY) (Kleczkowska et al., 1988; Linden et al., 1995).

The first reports of the effects of additional X chromosomes in males came from a series of large-scale prospective population-based studies in the United States and Europe during the 1970s. These groups of studies karyotyped over 200,000 live births, and then mapped the longitudinal physical, cognitive, and emotional development of the SCV individuals into adulthood (Nielsen and Wohlert, 1990; Ratcliffe et al., 1979; Robinson et al., 1983, 1990; Tennes et al., 1975).

Largely due to the rarity of 49,XXXXY, early prospective studies of the 1970s were confined to case studies. However, the findings were fairly consistent and indicated that 49,XXXXY is generally associated with severe developmental delays, such as learning and intellectual disabilities as well as speech and motor delays, and physical manifestations, most frequently affecting the skeletal, cardiac, and genital systems. Unlike other males with SCV such as Klinefelter syndrome, who are typically above average in height, 49,XXXXY patients often have decreased stature (Gropman et al., 2010; Linden et al., 1995; Ottesen et al., 2010; Visootsak et al., 2007). For a comprehensive review of the clinical phenotype, see Tartaglia et al. (2011).

Information about the impact of three extra X chromosomes on cognitive development is sparse. Linden et al. (1995) reported on 3 cases of 49,XXXXY identified as a part of the Denver prospective SCV study and indicated that these individuals had IQ scores that fell into the intellectually disabled range. More recent studies have utilized larger referred samples than the early prospective studies and have relied on parent report of adaptive function (e.g., Visootsak et al. (2007)). Together, these studies have indicated that both intellectual (Linden et al., 1995) and adaptive functioning skills (Visootsak et al., 2007) often fall into the intellectually disabled range. However, a recent study by Gropman et al. (2010) that utilized a nonverbal intelligence test (in lieu of a traditional IQ test that has both verbal and nonverbal components) reported relatively preserved nonverbal intelligence, although language skills still showed significant impairment (as assessed by standardized language testing).

There is even less information available about how 49,XXXXY affects brain anatomy. Head size tends to be smaller than average, suggesting that brain volumes are also likely to be smaller (Linden

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et al., 1995; Visootsak et al., 2007). Brain imaging studies to date have also been largely limited to case reports.

Linden et al. (1995) reported computerized tomography (CT) results from three 49,XXXXY subjects. The first was a 21-year-old male with an IQ estimated at 39, little speech, and a history of a seizure disorder, who was found to have diffuse atrophy of the cerebrum and cerebellum on CT performed at the age of 12. The second was a 27-year-old male with an IQ of 56 and was found to have mildly prominent ventricles. The third was a 15-year-old male with an IQ of 40 whose head size was at the 25th percentile, but whose CT was otherwise read as normal (Linden et al., 1995).

An MRI of a 12-year-old 49,XXXXY male demonstrated unilateral mild left colpocephaly and mild cerebral atrophy (Galasso et al., 2003). A 3-year-old male was found to have prominent ventricles, mild cerebral atrophy, and thin corpus callosum (Haeusler et al., 1992). A 1-year-old male with 49,XXXXY had extensive isolated and confluent lesions in the subcortical white matter; these lesions were hyperintense on T2-weighted and FLAIR images. This child also had prominent ventricles and thin corpus callosum (García-Cazorla et al., 2004). Most recently, MRI results from a 30-month-old male demonstrated regional periventricular white matter abnormalities with a posterior predominance that also involved the spinothalamic tracts; a thin corpus callosum was also demonstrated (Tabarki et al., 2012).

The largest 49,XXXXY imaging case series to date included three individuals studied at different ages (Hoffman et al., 2008). One subject who underwent MRI for significant developmental delay was scanned at 14 months of age and again at 20 months. Both exams were significant for cerebral atrophy, prominent lateral ventricles and third ventricle, and thin corpus callosum. There was patchy and confluent abnormal signal in the periventricular white matter, predominantly in the parietal and frontal lobes. The second subject was scanned at 7 years of age. He had mild colpocephaly, thin corpus callosum, and several foci of abnormal signal in the periventricular and subcortical white matter. The third case was an adult of 39 years, who underwent MRI following new onset of generalized tonic–clonic seizures. Findings included atrophy involving both the cerebrum and cerebellum, mild colpocephaly, and thin corpus callosum. Numerous focal lesions were present in the periventricular, deep, and subcortical white matter, many more than would be expected for an individual of his age.

The case reports above include the description of 6 patients who had MRI studies, which provide a much more detailed evaluation of the white matter than does CT. The abnormalities described in these patients with 49,XXXXY syndrome predominantly relate to white matter: there were discrete white matter lesions of both the focal and confluent/regional types; a thin corpus callosum reflects a generalized paucity of white matter in the cerebrum; and colpocephaly reflects selective underdevelopment of white matter in the posterior portions of the cerebrum. Atrophy of the cerebrum and/or cerebellum can also result from a white matter abnormality. All six of these patients had at least 2 of these types of abnormalities, and 1 had all of the above.

Previous studies in other sex chromosome variations also found an association of additional X or Y chromosomes with an increased risk of focal lesions in the white matter. In a sample of 20 males with XXY or XYY, 6 showed one or more focal white matter lesion, while no lesions were found in 26 healthy matched control subjects (Warwick et al., 1999). Among 5 children with SCV (one each with 47,XXX, 48,XXYY, and 49,XXXXY and two with 47,XXY), all of them had focal white matter lesions (García-Cazorla et al., 2004).

Based on these previously reported neuroanatomical findings, we hypothesized that we would find a similar pattern of abnormalities affecting white matter in this largest 49,XXXXY case series to date, and we sought to further characterize the frequency of these findings.

2. Materials and methods

2.1. Participants

49,XXXXY males were recruited from throughout the USA with the help of Neurodevelopmental Diagnostic Center for Young Children and a parent advocacy group, Klinefelter Syndrome and Associates (KS&A). Parents of 49,XXXXY subjects were interviewed by telephone and asked to report their child's health, developmental, and educational history. Children with severe head injuries or other conditions that might have affected gross brain development were not accepted into the study. Several 49,XXXXY males participated in the protocol but are not presented in this report because they were either too anxious to scan (n = 3), were unable to lie still in the scanner (n = 3) which produced excessive motion artifact, or had a ventriculo-peritoneal shunt to treat hydrocephalus (n = 1), resulting in 14 patients who met the inclusion criteria for this report. Four of these 49,XXXXY patients have a history of seizures, 2 of whom had experienced absence seizures and 2 had febrile seizures. No obvious brain abnormalities identified on the MRIs were common to these four patients.

The diagnosis of 49,XXXXY was confirmed with karyotype testing on all subjects. High resolution G-band karyotyping was performed on phytohemagglutinin-stimulated patient peripheral blood cultures. A minimum of 50 metaphases were analyzed, and 3 karyotypes per patient were produced (all karyotyping was performed by Quest Diagnostics or the Cytogenetics Laboratory, Department of Obstetrics and Gynecology, Georgetown University Hospital). Subjects were included on the basis of a 49,XXXXY karyotype and not on the presence of specific clinical features. The group consisted of nonmosaic 49,XXXXY males ranging in age from 5.1 to 17.2 years (Table 1). The ethnic composition of the group was 11 white, 1 Hispanic, 1 African-American, and 1 biracial. Nine subjects were right-handed, 3 were left-handed, and 2 were mixed-handed. None of the boys were born prematurely; they all had gestational ages of 37–42 weeks (gestational age was not reported for 1 of these boys). None of the boys were diagnosed in utero through amniocentesis; they were all diagnosed postnatally (range 0–60 months, mean 11.2 months).

Table 1
Demographics; cognitive and behavioral results.

	49,XXXXY		46,XY			
	Mean (SD)	N	Mean (SD)	N	t	P
Age, y	11.6 (4.7)	14	11.6 (4.5)	42	0.1	.961
Height, in	56.8 (9.9)	14	58.7 (10.1)	41	0.6	.529
Weight, lb	107.6 (71.5)	14	107.5 (49.8)	42	0.0	.995
Tanner stage	2.0 (1.3)	10	2.7 (1.4)	38	1.5	.161
SES	56.8 (23.9)	14	51.7 (21.3)	42	0.7	.484
Full scale IQ	60.9 (9.9)	8	114.9 (12.2)	41	13.5	<.001[a]
Verbal IQ	63.6 (11.4)	8	113.7 (14.6)	39	10.8	<.001[a]
Performance IQ	63.3 (9.0)	8	112.3 (12.3)	39	13.1	<.001[a]
ABAS composite GAC	61.9 (14.3)	8	111.4 (8.6)	11	8.7	<.001[a]
PPVT standard score	65.0 (19.9)	9				
PPVT age equivalent, y	5.2 (2.2)	10				
CBCL total problems	63.4 (7.7)	12	40.3 (8.7)	32	8.5	<.001[a]
CBCL internalizing	60.7 (7.7)	12	42.3 (7.6)	32	7.1	<.001[a]
CBCL anxious/depressed	57.3 (5.4)	12	50.8 (2.2)	32	4.1	.001[a]
CBCL withdrawn/depressed	59.5 (6.8)	12	51.0 (2.3)	32	4.2	.001[a]
CBCL somatic complaints	62.5 (8.3)	12	51.9 (4.2)	32	4.2	.001[a]
CBCL externalizing	59.8 (10.6)	12	43.3 (8.1)	32	4.9	<.001[a]
CBCL rule-breaking behavior	58.7 (7.1)	12	51.4 (3.0)	32	3.4	.005[a]
CBCL aggressive behavior	62.2 (9.9)	12	51.2 (3.3)	32	3.8	.003[a]
CBCL social problems	66.3 (7.2)	11	50.1 (2.6)	31	6.9	<.001[a]
CBCL thought problems	61.8 (10.0)	12	50.6 (2.0)	32	3.8	.003[a]
CBCL attention problems	59.7 (5.6)	12	50.8 (1.9)	32	5.4	<.001[a]

All cognitive and behavioral t-tests survived Bonferroni adjustment except rule-breaking behavior.

[a] Statistically significant.