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Brain Magnetic Resonance Imaging Findings in 49,XXXXY Syndrome

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Abstract

Klinefelter syndrome is a chromosomal disorder characterized by one or more supernumerary X chromosomes, in addition to the normal 46,XY male karyotype. Whereas classic Klinefelter syndrome (47,XXY) occurs in 1:400 births, the most severe Klinefelter variant (49,XXXXY) occurs in only 1:85,000 births. The degree of cognitive impairment, specific skeletal changes, and genital abnormalities in Klinefelter syndrome variants is thought to correlate with the number of additional X-chromosomes present. Magnetic resonance imaging studies in individuals with classic Klinefelter syndrome show smaller brain volumes, but magnetic resonance imaging data are lacking for individuals with rarer and more severe Klinefelter variants. We present case reports and magnetic resonance imaging studies on 3 individuals with 49,XXXXY. All 3 patients exhibited varying degrees of volume loss and abnormalities in white matter. Changes in white matter may represent a specific finding in patients with severe Klinefelter variants such as 49,XXXXY, and karyotype analysis should be considered in patients with unexplained white-matter disease, especially when developmental delay or genital abnormalities are present.

Introduction

The incidence of sex-chromosome aneuploidy is relatively common, and is thought to occur in approximately 1:400 births [1]. Classic Klinefelter syndrome is defined by the karyotype 47,XXY, and is characterized by long limbs, tall stature, hypogonadism, gynecomastia, and mild developmental delay [2]. Multiple, rare atypical forms of Klinefelter syndrome are attributable to additional copies of sex chromosomes beyond 47,XXY that represent unique clinical phenotypes [1,2]. In general, variants of Klinefelter syndrome with increasing X-chromosome polysomy display specific bony changes, short stature, and developmental delay. Cognitive studies estimate that each supernumerary X chromosome results in an additive 15-point reduction in intelligence quotient. The most severe X-chromosomal

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polysomy variant, 49,XXXXY, is associated with skeletal abnormalities such as short stature, delayed bone age, sclerotic cranial sutures, radioulnar synostosis, cubitus valgus deformity, scoliosis, mandibular prognathism, and clinodactyly [3]. The incidence of 49,XXXXY is estimated at 1 per 85,000–100,000 births [1]. Approximately 25% of individuals with 49,XXXXY are cryptorchid, and most have severe hypogonadism with a hypoplastic scrotum [4]. Hypotonia and microcephaly are also common. Developmental outcomes are variable, with ultimate adult intelligence quotients generally ranging from 20–70 [2].

Although 47,XXY was associated with a smaller brain volume on magnetic resonance imaging [5], the number of reports regarding magnetic resonance imaging findings in rare Klinefelter variants with higher degrees of X-chromosome polysomy is extremely limited. Given the unique clinical phenotypes associated with these Klinefelter variants and an association between increasing X-chromosome polysomy and phenotypic severity, further examination of such individuals is warranted.

We present case reports and brain magnetic resonance imaging studies on 3 individuals with 49,XXXXY. The first patient was referred for metabolic evaluation because of developmental delay and brain magnetic resonance imaging with extensive and confluent white-matter disease suggestive of leukodystrophy. The second and third subjects were derived from a behavioral phenotype study in males with sex chromosomal aneuploidies, who both had numerous, punctate foci of T₂ hyperintensity on brain magnetic resonance imaging, a nonspecific finding seen in some normal individuals who are typically much older than the subjects reported here [6,7]. Because all 3 of our patients had some degree of volume loss and white-matter abnormality on brain magnetic resonance imaging, we argue that these magnetic resonance imaging changes may represent an additional feature of this rare syndrome. Furthermore, we argue that karyotype analysis should be considered in unexplained patients of white-matter disease, especially when developmental delay or genital abnormalities are present.

Case Reports

Patient 1

This male patient was born to nonconsanguineous parents at term after a normal pregnancy and delivery, with a birth weight of 2.5 kg. When the child was unable to sit at age 10 months, he was referred for a neurologic evaluation, which indicated diffuse hypotonia and normal electroencephalogram findings. Brain magnetic resonance imaging performed at age 14 months indicated moderate ventriculomegaly with dilatation of the third and lateral ventricles, and a slightly thin body of the corpus callosum. In T₂-weighted images (Fig 1), there were extensive patchy and confluent areas of abnormal high signal intensity in the periventricular and deep white matter of the parietal and frontal lobes bilaterally, sparing the subcortical U-fibers. The white-matter changes did not demonstrate contrast enhancement or restricted diffusion. Magnetic resonance imaging of the brain favored a leukodystrophy, but was not specific for a particular etiology.

A retinal examination at age 15 months revealed no chorioretinitis. A brainstem auditory-evoked response at age 15 months was normal. Urine rapid antigen testing and a culture for cytomegalovirus produced negative results. Plasma serologies for cytomegalovirus, rubella, toxoplasmosis, and herpes simplex virus were also negative. Serum ammonia and thyroid-stimulating hormone levels were normal.

The patient was referred for metabolic evaluation at age 20 months. At that time, his growth parameters for length and head circumference were at the 25th and 5th percentiles, respectively. His weight was at <5th percentile (50th percentile for 11 months). He could walk independently, and spoke approximately 4 words. There was no developmental regression. His testes were descended bilaterally, and there was a small anal skin tag present. Serum electrolytes, blood urea nitrogen, serum creatinine, serum creatine kinase, and liver function tests produced normal results. Levels of plasma amino acids, lactate, pyruvate, and urine organic acids were normal. Repeated brain magnetic resonance imaging at age 20 months revealed few changes. Karyotype analysis revealed 49,XXXXY in 20/20 cells counted.

Patient 2

This patient was born with ambiguous genitalia, a penoscrotal web, and a small phallus. At age 6 weeks, a karyotype analysis revealed 49,XXXXY in 20/20 cells counted. His additional medical issues have included ligation of a patent ductus arteriosus, asthma, seizures, and ventriculoperitoneal shunt for hydrocephalus. Brain magnetic resonance imaging performed at age 7 years revealed an enlargement of the lateral ventricles with some volume loss in the periatrinal regions, and mild thinning of the corpus callosum. In addition, several punctuate foci of high signal intensity were present in the periventricular and subcortical white matter (Fig 2).

The patient attended special educational classes, and received interventional services for his global developmental delays. When he was 11 years of age, the Stanford-Binet Intelligence Scale (4th edition) indicated that he was functioning in the moderate-to-severe range of mental retardation. His verbal intelligence quotient score was 57, his performance intelligence quotient was 58, and his full-scale intelligence quotient was 47. Currently, the patient is 25 years old and takes phenytoin and testosterone supplementation.

Patient 3

This male patient was born at term after a normal pregnancy and delivery, with a birth weight of 2.58 kg. At age 8 months, he was referred for a genetic evaluation for hypotonia and micropenis. A chromosomal karyotype analysis confirmed the diagnosis of 49,XXXXY. He sat at age 12 months, crawled at age 18 months, walked independently at age 36 months, and spoke his first word at approximately 13 years of age. He also exhibits asthma and diabetes mellitus type 2. At age 39 years, he manifested a generalized tonic-clonic seizure. Brain magnetic resonance imaging at that time revealed volume loss and atrophy, both in the supratentorial brain and cerebellum, with an associated increase in ventricular size and thinning of the corpus callosum (Fig 3). The degree of volume loss was more prominent in the parietal lobes, with a slightly colpocephalic appearance of the lateral ventricles. In

addition, there were numerous, small foci of periventricular, deep, and subcortical white-matter T₂ hyperintensities, much more than expected for a patient of his age (Fig 3). None of the lesions demonstrated enhancement or restricted diffusion. Presently, the patient is 40 years old, lives in a group home, and is able to communicate his needs through sign words and short sentences.

Discussion

Brain magnetic resonance imaging studies on Klinefelter syndrome have provided evidence that sex-chromosome polysomy exerts specific effects on brain development. Individuals with XXX and XXY have smaller brain volumes, and XXY individuals have enlarged lateral ventricles [5,8]. Despite evidence of a dose-dependent effect of increasing X-chromosome polysomy in Klinefelter syndrome on phenotypic severity, the number of reports on brain imaging in patients with severe Klinefelter variants is extremely limited. Only 2 reports on brain magnetic resonance imaging in 49,XXXXY have been published. Galasso et al. reported on a 12-year-old boy with microcephaly, developmental delay, and seizure disorder, whose brain magnetic resonance imaging indicated left cortical atrophy and enlarged lateral ventricles [9]. Haeusler et al. reported on a 3-year-old boy who had hypoplasia of the corpus callosum and ventriculomegaly secondary to cortical atrophy [10]. Giedd et al. used magnetic resonance quantitative analysis and reported a global lobar volume loss in the brains of XXY individuals, with sparing of the parietal regions [8]. The clinical magnetic resonance imaging examinations in our patients were not conducive to quantitative morphometric analysis, but 2 of our patients clearly demonstrated a more prominent volume loss in the parietal and peritriangular regions of the brain (patients 1 and 3). Patient 3 also exhibited significant cerebellar atrophy, which was not present in previous imaging studies on 49,XXXXY or in our other 2 patients [9,10].

Although previous magnetic resonance imaging studies on rare Klinefelter variants did not describe abnormalities in white matter [9–11], the most striking finding of brain magnetic resonance imaging in our patients was the presence of white-matter disease. Some degree of white-matter T₂ signal abnormality was present in all 3 of our patients, ranging from extensive confluent white-matter disease (patient 1) to punctate foci of signal abnormality (patients 2 and 3). In the most severe patient (patient 1), an extensive evaluation provided no clinical or laboratory evidence for congenital infection, metabolic disease, or hypoxic-ischemic encephalopathy that could explain the magnetic resonance findings. Although punctate foci of T₂ hyperintensity are a nonspecific finding that can be present in normal elderly individuals, the degree to which they are seen in patients 2 and 3 is unusual, given the ages of these individuals (7 and 39 years, respectively). In several meta-analyses, T₂ hyperintensities were correlated with a loss of global cognitive functioning in nondemented aging individuals and patients with myotonic dystrophy [6,12]. Interestingly, Warwick et al. reported that multiple patients with XXX and XXY manifested “high intensity signal foci” on brain magnetic resonance imaging [5]. Given that many of the clinical findings of Klinefelter syndrome appear along a spectrum that correlates with the degree of X-aneuploidy, we propose that white-matter lesions may be part of this syndrome. Additional magnetic resonance imaging studies to address this issue are needed in individuals with rare Klinefelter variants. Longitudinal studies will also be necessary to increase our

understanding of the natural history of these T₂ signal abnormalities, and how they correlate with clinical features and cognitive profiling. Finally, screening for sex-chromosome aneuploidy by karyotype analysis with at least 50 cell counts to rule out mosaicism in the clinical setting of developmental delay and white-matter disease should be considered, especially when laboratory investigations do not reveal an obvious etiology, or other congenital anomalies are present.

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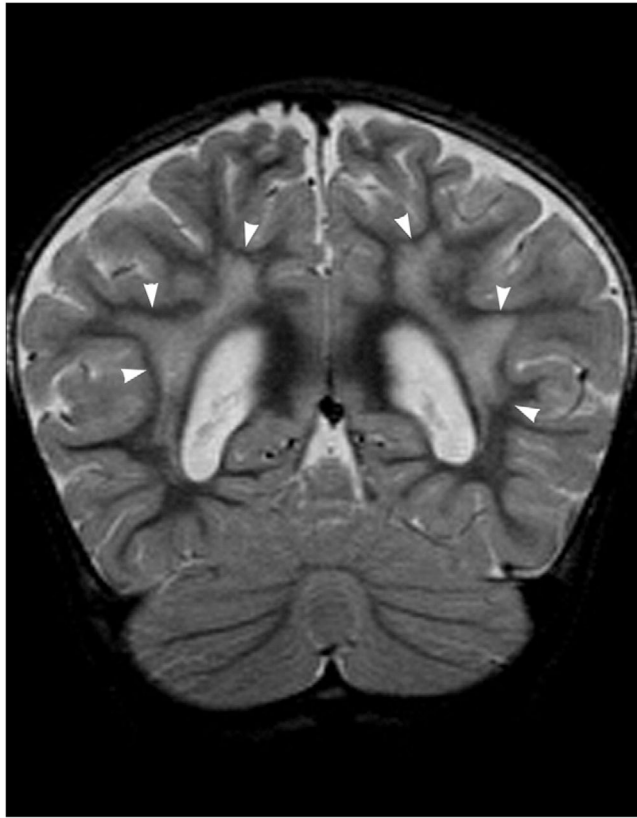


Figure 1. Brain magnetic resonance imaging of patient 1. Coronal T₂-weighted image of the brain demonstrates confluent areas of white-matter T₂ hyperintensity in the bilateral parietal regions, with sparing of subcortical U-fibers (arrowheads). Patchy areas of white-matter signal abnormality are present in the frontal lobes bilaterally, with bilateral ventricular enlargement.

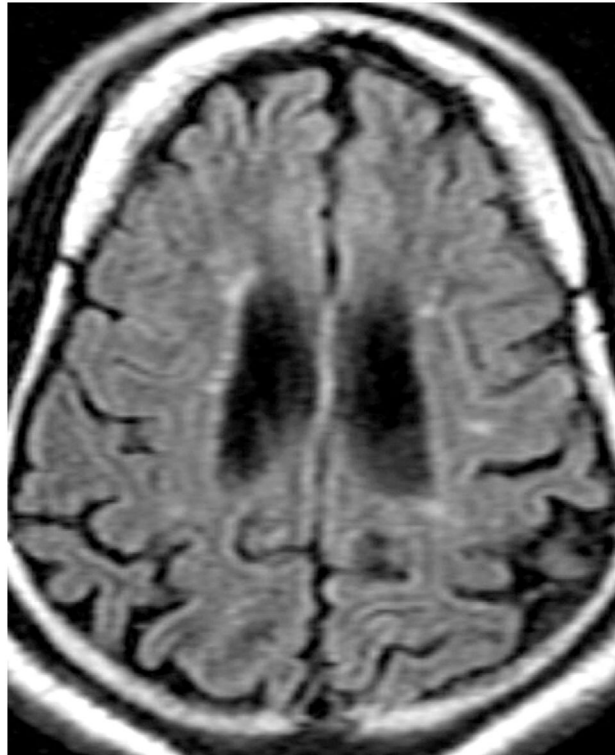


Figure 2. Brain magnetic resonance imaging of patient 2. Axial fluid attenuation inversion recovery (FLAIR) image demonstrates numerous punctate foci of high signal intensity in the periventricular white matter.

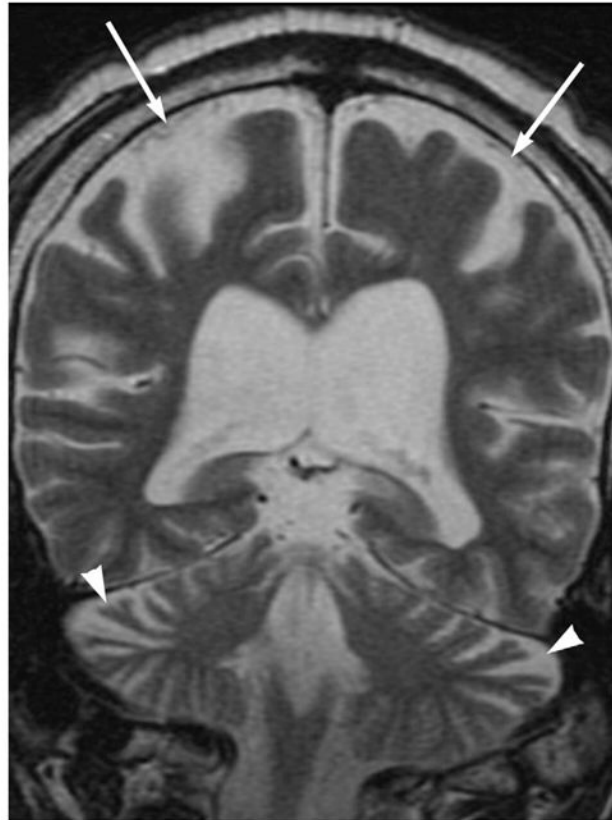


Figure 3.

Brain magnetic resonance imaging of patient 3. Coronal T₂-weighted image of the brain demonstrates global volume loss, most prominently in the parietal lobes (arrows), with enlargement of the lateral ventricles. There is also volume loss in the cerebellum (arrowheads) and scattered punctate foci of T₂ signal hyperintensity in the white matter. Sagittal T₁-weighted images demonstrated associated thinning of the corpus callosum (not shown).