

Musculoskeletal Anomalies in a Large Cohort of Boys With 49, XXXXY

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49, XXXXY is a rare aneuploidy and variant of Klinefelter syndrome, occurring in 1 per 80,000–100,000 live births. We present a cohort of 40 affected males, focusing on musculoskeletal problems. Subjects were participants in an annual 49er family support group meeting. Children were examined in a multidisciplinary clinic by a pediatric neurologist and geneticist, a pediatric orthopedist, a neurodevelopmentalist, and two physical therapists. The patient data were collected from this clinic from 2004 to 2012. All patients were required to have karyotypes that confirmed the presence of XXXXY. There was a high prevalence of musculoskeletal disorders, particularly hypotonia (34 patients [85%]), radioulnar synostosis (30 [75%]), pes planus (26 [65%]), asymmetric hip rotation (27 [67.5%]), and clinodactyly (24 [60%]). Other, less common lower-extremity disorders, included, 5 patients (12.5%) with unilateral club foot, 5 boys (12.5%) with pes cavus, 10 patients (25%) genu valgum and 2 children with genu varus (5%). To our knowledge, this is the first large cohort of boys with 49, XXXXY that focuses on musculoskeletal disorders. There was an increased incidence of hypotonia, clubfoot, avascular necrosis of the femoral head, radioulnar synostosis, and pes planus compared to the normative population. Boys with 49, XXXXY

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would benefit from multidisciplinary evaluations, particularly from pediatric orthopedists, physical therapists, neurologists, and geneticists for appropriate medical care. © 2013 Wiley Periodicals, Inc.

KEY WORDS: XXY, 49; XXXXY; Klinefelter syndrome; orthopedic anomalies; sex chromosome variations; X and Y chromosomal variations; musculoskeletal deformities

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INTRODUCTION

In 1942, Harry Klinefelter described a common set of symptoms in nine men, the majority of whom possessed testicular dysgenesis, elevated urinary gonadotropins, eunuchoidism, azoospermia, and gynecomastia [Klinefelter et al., 1942]. Although originally described as an endocrine disorder with a testosterone deficiency, Klinefelter syndrome was found to be the result of an additional X chromosome (XXY) [Jacobs and Strong, 1959]. 49, XXXXY results from the nondisjunction of the X chromosome during both meiosis I and meiosis II [Visootsak, 2006]. The rarest of the sex aneuploidy conditions, it was first described in 1960 [Fraccaro et al., 1960].

49, XXXXY occurs in 1 per 80,000–100,000 births; XXY, by contrast, occurs in 1 per 500–650 live births [Fraccaro et al., 1960; Barr et al., 1962; Cammarata et al., 1999; Simpson et al., 2003; Visootsak, 2007]. 49, XXXXY has become known as a severe variant of Klinefelter syndrome due to its characteristic features, central nervous dysfunction, congenital anomalies, and global developmental delays [Barr et al., 1962; Linden et al., 1995; Peet et al., 1998; Visootsak, 2007].

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At birth, subtle facial dysmorphism may be noted, such as epicanthal folds,

upslanting palpebral fissures, or full upper eyelids [Simpson et al., 2003; Visootsak, 2007; Gropman et al., 2010; Samango-Sprouse et al., 2011; Tartaglia et al., 2011]. Associated orthopedic abnormalities include congenital hip dysplasia, torticollis, radioulnar synostosis, congenital talipes equinovarus (club foot), and clinodactyly [Barr et al., 1962; Okuyama, 1993; Linden et al., 1995; Cammarata et al., 1999]. As the boys mature, delay in motor and speech, along with other cognitive deficits and behavioral problems, are frequently reported. In addition, multiple orthopedic problems, including congenital hypotonia, radioulnar synostosis, tibulofibular synostosis, pes planus or pes cavus, avascular necrosis of the femoral head, or spinal deformities, may be noted [Dallapiccola and Pistocchi, 1968; Schmidt et al., 1978; Peet et al., 1998; Cammarata et al., 1999; De Rosa et al., 2001; Nishimura et al., 2008]. Orthopedic abnormalities affect activities of daily living, mobility, neurodevelopmental progression, and ultimately, quality of life. In an effort to aid clinicians and families with the early identification of musculoskeletal anomalies, this article sought to survey the common musculoskeletal anomalies in this population and to expand data on birth weight, birth height, etc., that have been previously presented by Gropman et al. [2010].

MATERIALS AND METHODS

Patients

All patients were participants in an “Annual 49er’s Meeting” at the Neurodevelopmental Diagnostic Center for Young Children (NDCYC) in Davidsonville, MD. All participants in the annual conferences were evaluated at least once in a multidisciplinary clinic that

was conducted during consecutive summers from 2004 until July 2012. The team included a pediatric neurologist/geneticist (AG), a neurodevelopmental specialist (CASS), a pediatric orthopedist (LT), and two physical therapists (FM and RP). All available medical records were reviewed. Institutional Review Board approval, which included the patient examination and retrospective chart review, was obtained. All parents signed informed consents for their sons to be evaluated. All study participants had confirmed genetic documentation of their karyotype consistent with 49, XXXXY.

Evaluations

Neurological evaluation

The 40 participants had a pediatric neurological evaluation tailored to age by a neurologist/geneticist (AG) and a neurodevelopmental specialist (CASS), including mental status, muscle tone, motor strength, adventitious movements (presence/absence of tremors), reflexes, gait, and balance.

Orthopedic evaluation

An orthopedist (LT) specializing in care of children with complex disorders examined all 40 participants. Examination included visual inspection, joint range of motion, motor strength, and gait observation. Radiographs were not available for most participants.

Physical therapy evaluation

Physical therapy evaluations were conducted by licensed physical therapists (FM and RP) who assessed muscle tone, movement patterns, strength, gait and range of motion. Both therapists have extensive experience in the assessment and care of individuals with neurodevelopmental disorders.

RESULTS

Patient demographics are presented in Table I. Average age was 63 months (range 8–174 months) Thirty-four of the patients were Caucasian, three were Hispanic, two were African American, and one was Southeast Asian. Six of the participants resided outside the United States (three from Canada, and one each from Italy, England, and Honduras).

The average paternal age was 34 ± 7.03 years and the average maternal age was 31 ± 5.46 years at time of delivery, which is older than the mean age (25.4 years) of childbirth in the United States [Martin et al., 2012]. The average birth weight was 2.52 ± 0.44 kg (5th centile), with a range of 1.7–3.7 kg. The average gestational age was 37.1 ± 2.25 (n = 31) months with a range of 33–42 weeks, there were eight known children delivered prematurely. The average length at birth was 46.69 ± 2.70 cm (10th centile), with a range of 39–51 cm [Martin et al., 2012]. Fifty-eight percent of the deliveries were cesareans; higher than the average US rate, which, according to the most recent report from the Centers for Disease

Control and Prevention, was 33% [Hamilton et al., 2011].

The mean age at diagnosis was 4 months (range: neonatal to 16 months). Typically children were first evaluated because of parental concerns regarding dysmorphic features, developmental delay, and/or microphallus.

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General appearance included a characteristic facial appearance (upslanting palpebral fissures, hypertelorism, synophrys, and arched eyebrows) (Fig. 1). Less common clinical features included cleft lip and palate (three participants) and ear malformations (ear tag, abnormal helix) in five children.

The average head circumference was 32.64 ± 1.46 cm (7.5th centile), with a range of 30–36 cm.

Eighty-five percent of patients had generalized hypotonia (Table II). Tonus was decreased equally in the trunk, extremities, and oral facial musculature. Motor milestones were delayed in all patients; the average age at independent ambulation was 25.5 months (range 16–27 months).

Anomalies of the upper extremities were the most common among the participants (Table II). Clinodactyly was present in 60% participants. Loss of pronation and supination of the forearm, consistent with radioulnar synostosis, was noted in 75% of patients (Fig. 2). In addition, 32.5% had palpable radial head subluxation or dislocation.

Approximately 27.5% had a history of torticollis; all had been treated with physical therapy. Spinal abnormalities were uncommon (Table II). Increased lumbar lordosis was noted in 7.5% of patients, and there was a low incidence of scoliosis (5%) and kyphosis (2.5%).

Approximately 7.5% of patients had a history of developmental dysplasia of the hip, and 10% had X-ray

TABLE I. Patient Characteristics and Demographics of the Study Population (N = 40)

Patient characteristics	N	Mean	Median	Range	Centile
Age at diagnosis	16	4 months	4 months	1–16 months	
Age at first evaluation	40	63 months	55.5 months	8–174 months	
Gestational age	31	37.1 ± 2.25 weeks	37 weeks	33–42 weeks	
Birth weight	39	2.5 ± 0.45 kg	2.4 kg	1.7–3.7 kg	5th
Birth length	35	46.7 ± 2.70 cm	47.00 cm	39–51 cm	10th
Birth head circumference	27	32.6 ± 1.46 cm	32.4 cm	30–36 cm	7.5th
Patient demographics	N	Mean	Median	Range	
Maternal age at birth	38	31 ± 5.46 years	32	21–46 years	
Paternal age at birth	38	34 ± 7.03 years	33	23–65 years	
Ethnicity	40		Percent of total population		
Caucasian	35		88%		
Indian	1		2.5%		
African American	2		5%		
Hispanic	2		5%		
Delivery method					
Cesarean	22		58%		
Vaginal	15		39%		



Figure 1. The photo depicts a 10-year-old boy with 49,XXXXY and shows the characteristic facial features including hypertelorism and upslanting palpebral fissures.

confirmation of unilateral avascular necrosis of the hip (Legg–Calve–Perthes) (Fig. 3). Asymmetric rotation of the hips was displayed in 67.5% of the participants, characterized by reduced internal rotation, usually on the left. Of the children, 12.5% had a history of unilateral clubfoot. Sixty-five percent children had pes planus, while only 12.5% had pes cavus. Twenty-five percent of the children had genu valgum, and 5% had genu

varum. Twenty-two percent had leg-length discrepancies (Table II).

Motor testing revealed significant asymmetry with shortened musculature in the pelvic region and upper trunk. Gait was characterized by a shortened stride with overutilization of extension and decreased truncal rotation and flexion. Dexterity and fine motor skills were more intact than locomotion and balance but were delayed in comparison to

boys with 47, XXY and neurotypical children.

DISCUSSION

49, XXXXY is the most rare variant of Klinefelter syndrome and to our knowledge; this is the largest cohort of males with 49, XXXXY assembled to date. This is also the first report focused exclusively on the musculoskeletal abnormalities of these children.

Seventy-five percent of the participants in our study had clinical evidence of radioulnar synostosis; this rate is far higher than 50% prevalence reported in previous studies [Zaleski et al., 1966; Schmidt et al., 1978; Jones, 2006].

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Although radioulnar synostosis is typically treated with observation, this group of patients may present a unique challenge for orthopedic surgeons; for example, one older boy in our study, who had obvious bilateral radial head dislocations, complained of pain and difficulty with activities of daily living. Studies are needed to better track the natural history of this disorder as well as to explore surgical interventions that might preserve or improve existing function and comfort.

Hip disorders were also common in this cohort. Three children had hip dysplasia identified in infancy, a disorder which is typically far more common in girls. In addition, four (10%) children had radiographically confirmed avascular necrosis (AVN) of the femoral head, and 67.5% had asymmetric hip rotation (but otherwise asymptomatic). Previous authors have reported rates of AVN as high as 25% [Jones, 2006]. The lower incidence in our cohort may reflect the

TABLE II. Orthopedic Abnormalities (N = 40)

Orthopedic diagnosis	N	%
Congenital talipes equinovarus (CTEV)	5	12.5
Hypotonia	34	85
Torticollis	11	27.5
Clinodactyly	24	60
Radioulnar synostosis	30	75
Anterior/posterior radial head dislocation	13	32.5
Lordosis	3	7.5
Scoliosis	2	5
Kyphosis	1	2.5
Total spine abnormalities	6	15
Leg length discrepancy	9	22.5
Avascular necrosis of femoral head	4	10
Hip dysplasia	3	7.5
Asymmetric hip rotation	27	67.5
Genu varus	2	5
Genu valgum	10	25
Tibulo-fibulo synostosis	4	10
External tibial torsion	5	12.5
Internal tibial torsion	0	0
Pes cavus	5	12.5
Pes planus	26	65



Figure 2. A–D: The radiographs depict radioulnar synostosis in boys with 49, XXXY; subpart D shows radial head dislocation as well in one boy.



Figure 3. Hip films of a 9-year-old boy with 49, XXXY; the radiographs show small femoral heads bilaterally, far worse on the left. This was interpreted as epiphyseal dysplasia with secondary avascular necrosis on the left (similar to Legg–Calve–Perthes disease); subsequently this progressed to left femoral head collapse requiring extensive orthopedic surgical intervention.

young age of our patient group (average 63 months), and future evaluation with X-rays may demonstrate that this number should be much higher.

The boys also displayed a wide range of other musculoskeletal anomalies: moderate hypotonia, leg-length discrepancies (not caused by hip dysplasia), pes planus, club foot, and genu valgum. Such abnormalities affect gross motor development, ambulation, and stride. Efforts to mitigate their impact through physical therapy, orthotics, and exercise should be utilized throughout their lifetime.

This study has several limitations. First, although this is the largest cohort reported to date, there were only 40 patients due to the rarity of this disorder. Second, the patients were seen outside a hospital, so X-rays were generally not available. Third, some data fields are incomplete as some parents were not knowledgeable of their child's complete history. Most important, the majority of the study cohort was very young, and additional musculoskeletal problems may be revealed as they age.

In summary, this article reports on the orthopedic anomalies associated with 49, XXXXY. The high incidence of these problems suggests a need for routine evaluations by a multidisciplinary team experienced with complex neurodevelopmental disorders. Attention should be directed at identification of musculoskeletal anomalies that might influence motor development; such as radioulnar synostosis, avascular necrosis of the femoral head, torticollis, club foot, and genu valgum. Anticipatory guidance should be provided to parents of boys with 49, XXXXY regarding the need for orthopedic mentoring during growth and development.

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