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Timing of Diagnosis of 47,XXY and 48,XXYY: A Survey of Parent Experiences

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Abstract

47,XXY/Klinefelter syndrome is the most common sex chromosomal aneuploidy, yet 64% of males with this condition go undiagnosed. 48,XXYY is less common and there is less known about the diagnosis. The objective of this study is to describe the diagnosis experiences of parents of males with 47,XXY and 48,XXYY. Parents of 89 males with 47,XXY and 76 males with 48,XXYY completed a survey that gathered data about their experiences leading to a diagnosis, including the current age of the child, age at diagnosis, reasons for initial concern, and the specialists providing the diagnosis. In the 47,XXY cohort diagnosed postnatally, 59% presented with developmental delay, with a mean age at first parental concern of 5.2 years and mean age of diagnosis at 10.0 years. The remaining 41% presented with endocrinologic issues with a mean age at first concern of 19.1 years and mean age of diagnosis at 21.1 years. In the 48,XXYY group, 93% presented with developmental delay, with mean age at first parental concern of 2.4 years and mean age of diagnosis at 7.6 years. Hence, the average time from initial parental concern to diagnosis of 47,XXY or 48,XXYY ranges from 2 to 5 years, with those presenting with developmental issues having a longer lag to diagnosis compared to those presenting with endocrinologic issues. Increased awareness of the developmental, psychological, and medical features of 47,XXY and 48,XXYY is important to facilitate timely diagnosis and initiation of appropriate screenings and treatments that are important for optimal outcomes.

Keywords

Sex chromosomal aneuploidies; delayed diagnosis; medical support

INTRODUCTION

The prevalence of 47,XXY, also known as Klinefelter syndrome, is estimated to be between 1 in 581 to 1 in 917 males, making it the most common sex chromosome aneuploidy (SCA) in humans [Coffee et al., 2009; Morris et al., 2008]. Children with 47,XXY are at increased risk for developmental delays, speech-language disorders, learning disabilities, attention deficit hyperactivity disorder (ADHD), and other psychological conditions, although there is wide variability in the presence and severity of neurodevelopmental and psychological

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problems. Medically, 47,XXY is associated with hypergonadotropic hypogonadism which usually becomes clinically significant by mid-puberty, leading to the need for testosterone replacement therapy.

Despite the high incidence of 47,XXY, the majority of males with 47,XXY are not diagnosed in their lifetime. A study from the United Kingdom comparing the number of anticipated cases in a birth cohort to the number of cases actually ascertained by genetic testing estimated that 10% of cases are diagnosed by prenatal amniocentesis and 26% are diagnosed postnatally during childhood or adulthood when they present with clinical features, such as developmental delay, behavioral problems, hypogonadism, gynecomastia, or infertility. The remaining 64% of males with 47,XXY are never diagnosed. Of those diagnosed postnatally, only 28% were diagnosed in childhood or adolescence, with the remainder diagnosed in adulthood, primarily due to hypogonadism or infertility [Abramsky and Chapple, 1997]. A similar study from Denmark found comparable results that revealed approximately 75% of cases of 47,XXY are undiagnosed (or 1.2 million males across Europe), and less than 10% of cases are identified before puberty [Bojesen et al., 2003]. Similar studies to determine ascertainment rates of 47,XXY or other SCA have not been undertaken in the United States; however, genetic testing practices are similar, and ascertainment rates are far below the estimated 285,000 American males with 47,XXY [Moeschler and Shevell, 2006].

While 47,XXY is the most common sex chromosomal condition, mosaic patterns (46,XY/47,XXY) and additional X's and/or Y's, such as 48,XXYY, 48,XXXY, and 47,XYY, do occur, albeit less frequently than 47,XXY. The prevalence of 48,XXYY is approximately 1 in 18,000 to 1 in 40,000 males [Muldal, 1960; Sorensen et al., 1978]. Although physical characteristics are similar to 47,XXY (e.g., tall stature and hypergonadotropic hypogonadism), 48,XXYY syndrome is typically associated with more significant neurodevelopmental involvement and increased risk for other medical problems such as seizures and hypothyroidism [Tartaglia et al., 2011; Tartaglia et al., 2008; Visootsak and Graham, 2009; Visootsak et al., 2007]. Thus, ascertainment of cases of 48,XXYY is important so that optimal medical and psychological screenings and interventions can be provided.

In a study of 95 males with 48,XXYY ranging from 1 to 55 years (mean age of 14.9 years), approximately 37% (35/95) were diagnosed between 1–5 years of age, 25% (23/95) between 6–10 years, and 27% (26/95) after 11 years of age. Compared to 47,XXY, cases with a prenatal diagnosis of 48,XXYY are rare (2/95), and 68% of cases were ascertained due to developmental and behavioral features, whereas 30% were identified for endocrinology concerns [Tartaglia et al., 2008]. Due to the rarity of 48,XXYY syndrome, prospective newborn screening studies and studies that compare birth prevalence to ascertained cases are unavailable but a large percentage of cases are likely undiagnosed. However, because of the more significant neurodevelopmental involvement and increased rate of congenital anomalies and dysmorphic features, it is likely that a higher percentage of individuals with 48,XXYY are ascertained compared with 47,XXY.

In order to further explore factors leading to the diagnosis of 47,XXY and 48,XXYY, we surveyed parents to obtain information about their experiences in obtaining the diagnosis. We evaluated initial parental concerns and the timing of chromosomal karyotype testing that led to the diagnosis of 47,XXY or 48,XXYY. The results are important in helping us understand parental experiences in obtaining the diagnosis and call attention to factors leading to a timely diagnosis.

MATERIAL AND METHODS

Participants

Study participants were parents or guardians of males with 47,XXY who were identified at the American Association for Klinefelter Syndrome Information and Support or Klinefelter Syndrome and Associates family conferences, or at the University of California Davis or Children's Hospital Colorado genetics, developmental pediatrics, or endocrinology clinics. Additionally, parents or guardians of males with 48,XXYY were recruited from *The XXYY* Project, an organization that supports individuals with 48,XXYY syndrome, or at the University of California Davis or Children's Hospital Colorado clinics.

Procedures

After receiving approval from the University of California Davis and University of Colorado institutional review boards, we recruited parents or guardians of individuals with a diagnosis of 47,XXY or 48,XXYY. Informed consent was obtained from all participants. Parents provided information about the child's gender, age, and genetic status. Parents completed a 10-item survey asking about age at initial concerns, the first signs or symptoms concerning to the parent (e.g., development, learning, physical features), professional verification of concerns, age of diagnosis, and the type of medical specialist who ordered genetic testing.

Statistics

Data from the demographic questionnaire were analyzed using descriptive statistics. For the different variables (e.g., current age, age of first concern) as indicated in Table I, descriptive statistics, including mean, range, and standard deviations of each continuous variable, were computed for the 47,XXY and 48,XXYY groups using SAS, version 9.1 software (Cary, NC), allowing for inspection and direct comparison.

RESULTS

A total of 165 individuals participated in the study, including the parents of 89 individuals with 47,XXY and 76 with 48,XXYY. Of the total sample for 47,XXY, 51% (n = 45) were diagnosed prenatally. Males who were diagnosed postnatally (n = 44) had a mean current age of 23.2 years (range 16 months – 55 years, standard deviation (SD)±13.0). Participants with 48,XXYY included parents of 76 males with a mean current age of 14.3 years (range 3 – 36 years, SD±8.0). Seventy-three males with 48,XXYY received the diagnosis postnatally and 3 males were diagnosed prenatally. For the purposes of this study, only males who were postnatally diagnosed were included in subsequent data analysis.

In the postnatally diagnosed cohort with 47,XXY (Table I), we separated the cohort into two groups based on initial parental concerns: 1) initial concern over neurodevelopmental features (e.g., developmental delay, learning, or behavioral problems) or 2) initial concern over endocrinologic issues (e.g., incomplete pubertal development, microorchidism, gynecomastia).

The first group presenting with neurodevelopmental problems consisted of 26 males (mean current age 15.9 years, range 1.6–55 years, SD±12.9); their mean age at first parental concern was 5.2 years (range 2 months–20 years, SD±5.5) and mean age of diagnosis was 10.0 years (range 2 months–30 years, SD±9.8). Chromosomal karyotype testing was ordered by pediatricians for nine participants, geneticists for six cases, and neurologists for three cases. In seven cases the parents were initially concerned about the child's developmental issues; however, the diagnosis was not made until physical features (e.g., microorchidism, lack of pubertal development) became evident, prompting referrals to endocrinologists who

subsequently ordered chromosome testing and received the diagnosis between the ages of 8 months to 34 years. In one case, the initial parental concerns of low muscle tone and speech delay did not prompt testing; however later symptoms concerning for leukemia led to the pediatric oncologist ordering a bone marrow biopsy, which yielded the diagnosis of 47,XXY at age 2 years.

The second group consisted of 18 males with 47,XXY (mean current age of 32 years, range 16–59 years, SD±13.2) with first concerns related to endocrinologic issues (e.g., microorchidism, delayed or slowed progression of puberty, gynecomastia) at a mean age of 19.1 years (range 3 months–40 years, SD±9.7) and mean age of diagnosis at 21.1 years (range 7 months–40 years, SD±8.9). Nine males were reportedly diagnosed with 47,XXY by an endocrinologist, four by primary care doctors, two by geneticists, two by urologists, and one by a psychologist. In the cohort presenting with endocrinologic issues, approximately 80% (15/18) of parents reported they were unaware of their child's lack of pubertal development or microorchidism, and routine physical examination by their physician led to genetic testing for 47,XXY.

The 48,XXYY group consisted of parents of 73 males, with three being diagnosed shortly after birth based on dysmorphic features. The remaining 70 males all presented with initial concerns of developmental delay or hypotonia based on parental report, with mean age at first parental concern of 2.4 years (range 1 day–7 years, SD±3.1) and mean age of diagnosis at 7.6 years (range 2 days–28 years, SD±5.7).

DISCUSSION

This study describes parents' experiences in obtaining a diagnosis for their male children with 47,XXY and 48,XXYY. For both groups, we noted a common finding of delayed diagnosis, especially in individuals presenting with concerns of developmental delays or behavioral difficulties. Similar to previous reports, our study concludes that 47,XXY is diagnosed based on the presence of a variety of signs and symptoms, including developmental delay, learning or behavioral problems, hypogonadism, gynecomastia, or lack of progression of pubertal development [Abramsky and Chapple, 1997; Visootsak and Graham, 2009], whereas 48,XXYY syndrome is most commonly diagnosed as a result of developmental delays or behavioral concerns [Tartaglia et al., 2008].

Males with 47,XXY may present with nonspecific findings at birth, such as hypotonia or fifth digit clinodactyly; however, the lack of distinct physical features at birth arouses little suspicion of a genetic disorder for pediatricians. Presenting concerns that prompt a diagnosis in the pediatric population most commonly fall into one of two categories: (1) developmental-behavioral issues, such as speech delays, behavioral problems, and learning disabilities, or (2) endocrinologic issues related to hypogonadism, such as microorchidism, lack of progression of pubertal development, or gynecomastia. The concomitant presence of tall stature and/or long limbs occasionally prompts genetic testing, but tall stature and/or long limbs alone rarely lead to clinical suspicion of 47,XXY. The developmental-behavioral features can vary greatly between individuals with 47,XXY; however, prospective studies of infants with 47,XXY identified via newborn screening and followed into adulthood showed that approximately 70–80% had early delays in speech and/or motor milestones, and approximately 80% required special education support in the school setting, most commonly for reading and language-based learning disabilities [Bender et al., 1986; Graham et al., 1988; Rovet et al., 1996]. Postpubertal microorchidism is almost universal among patients with 47,XXY, and most males with 47,XXY require testosterone replacement therapy starting in mid-adolescence to support pubertal development, muscle strength and endurance, and bone health. Thus, while physical and neurodevelopmental features of

47,XXY are present in the majority of pediatric and adolescent individuals with the condition, most are not being ascertained in this time period.

Interestingly, in our cohort there was considerable variability in the age of diagnosis for males with 47,XXY. For those diagnosed in the postnatal period due to developmental delays, parental concerns arose on average 4.8 years before a professional ordered a karyotype. Despite expressing their worries about their child's development and/or behavior, parents often reported that the primary care physicians had reassured them their son would catch up with their developmental skills, or they were advised to "wait and see," since "boys often develop at a slower pace." These findings are troubling and subject to recall bias; however, previous prospective studies show that approximately 80% of males with 47,XXY have developmental delays or language-based learning disabilities, and a more timely diagnosis upon presentation of developmental concerns would maximize the benefit of early intervention programs, educational resources, and medical treatments (e.g., testosterone supplementation).

For some individuals, the primary care physicians responded to parental concerns about neurodevelopmental or behavioral problems by making appropriate referrals to speech therapy or other early intervention or school programs; however, many parents reported that the primary care physicians did not initially attempt to pursue a medical diagnosis (e.g.,karyotype or other genetic testing) or refer their child to a specialist (e.g., developmental-behavioral pediatricians, neurologists, geneticists) to investigate the cause of their child's developmental delay, learning and behavioral problems. In approximately 35% (9/26) of those diagnosed, it was the general pediatrician who ordered the chromosomal testing, with the remaining 65% diagnosed by a specialist (e.g., endocrinologists, geneticists, and neurologists). The most current American Academy of Pediatrics [2006] recommendations on the genetic evaluation of children with developmental delays or intellectual disabilities include chromosome analysis for children with developmental delays in more than one domain and in children with intellectual disability [Moeschler and Shevell, 2006]. Unfortunately, these recommendations are likely to significantly underestimate cases of 47,XXY, since isolated delays in speech-language abilities or mild to moderate language-based learning disabilities are much more common than intellectual disability.

In contrast, diagnosis was delayed by only 2.0 years for those with 47,XXY presenting with endocrinologic issues. Although a delay of 2.0 years is certainly better than the 4.8-year delay with the presentation of neurodevelopmental problems, it is still a great amount of time, given that these males most typically present in adolescence or young adulthood, when they likely have testosterone deficiency and need evaluation for testosterone replacement therapy. Testosterone deficiency secondary to testicular dysgenesis in 47,XXY and 48,XXYY can lead to incomplete pubertal development gynecomastia and decreased strength/physical endurance in adolescence, and also contributes to other medical problems, such as osteoporosis, and sexual dysfunction in adulthood [Horowitz et al., 1992]. Additional studies support testosterone therapy as helpful for self-esteem and general wellbeing in adults with 47,XXY [Nielsen et al., 1988]. Thus, earlier identification of 47,XXY and 48,XXYY would allow the monitoring of pubertal progression and testosterone levels to permit timelier initiation of testosterone replacement therapy.

In males with 48,XXYY, parents expressed concern over developmental issues at an earlier age (mean 2.4 years) than the 47,XXY group (mean 5.2 years), which is consistent with the behavioral phenotype of 48,XXYY being associated with more significant neurodevelopmental and psychological difficulties [Tartaglia et al., 2011; Visootsak et al., 2007]. Despite their concerns coming earlier than the 47,XXY group, there was still an average gap of 5.2 years from the time of concern to diagnosis. Reminiscent of the 47,XXY

experiences, parents described that primary care providers offered reassurances to parents when they expressed concerns about their son's developmental delays or behavioral difficulties, and a medical etiology was not pursued until approximately five years later, on average. Since males with 48,XXYY have more issues with development and behavior, 96% of our participants were diagnosed based on these presenting neurodevelopmental concerns, rather than endocrinologic issues.

The results of our study confirm that receiving a diagnosis of 47,XXY and 48,XXYY takes a long time from the time of initial parental concern. The difference in the amount of time from initial parental concern to SCA diagnosis leads us to speculate that pediatricians and other primary care providers may not associate neurodevelopmental or learning problems with SCA or other genetic disorders, or they may lack a sense of urgency to pursue further testing to investigate the cause for the child's delay. While they may refer for speech or motor evaluations and therapy, they may not pursue genetic testing or refer the child to a specialist in genetics, developmental-behavioral pediatrics, or neurology. Interestingly, when the pediatricians noted endocrinologic findings on their physical examination (e.g., lack of pubertal progression or microorchidism), they typically include 47,XXY or 48,XXYY as part of their differential diagnosis because of the more specific symptoms, and are much quicker to order genetic testing or refer the child to an endocrinologist. This suggests that primary care providers are more likely to suspect SCA when males present with endocrinologic issues, leading to a more timely diagnosis.

A later diagnosis is worrisome since earlier identification of SCA allows a child to optimally benefit from early intervention, screenings and treatments for learning and/or emotional disorders, access to other resources, and also alleviates potential parental stress associated with the diagnostic odyssey. Our findings support recommendations that primary care providers conduct a developmental screening and elicit parental concerns at every well child care visit. SCA should be included in the differential diagnosis of children presenting with developmental or behavioral concerns, and genetic testing to identify an etiology of delays should be pursued in addition to referrals for speech, motor, and/or educational therapies.

Limitations of this study include a small sample size that may not be representative of the spectrum of individuals with 47,XXY and 48,XXYY. All of our participants were recruited through the national SCA support organizations or SCA specialty clinics at UC Davis and University of Colorado. It is possible that their experiences differ from those who are unlikely to participate in support organizations and/or attend a SCA specialty clinic. Our sample may be biased in that it represents a group of parents who are active in the SCA community and proactive in seeking specialty clinic care for their child. Additionally, there may be recall bias when parents complete the questionnaires. We also did not collect parental socioeconomic status which may contribute to factors in accessing medical care and education. Yet, parents generally encounter similar barriers to the diagnosis. Our results are similar to reported experiences of families in previous studies, where the majority of males with SCA are not diagnosed in a timely fashion [Abramsky and Chapple 1997; Herlihy et al., 2011; Tartaglia et al., 2008].

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Table I

1) Mean age of initial parental concerns about development or endocrinologic issues, 2) mean age of diagnosis of sex chromosome aneuploidy, and 3) difference in age from first parental concern to diagnosis.

	47,XXY (*n* = 44)		**48,XXYY (*n* = 70)**
	Developmental concerns *n* = 26 Mean Age in Years (range)	**Endocrinologic issues *n* = 18 Mean Age in Years (range)**	**Developmental concerns *n* = 70 Mean Age in Years (range)**
First Concern	5.2 (2 months–20 years)	19.1 (3 months–40 years)	2.4 (1 day–7 years)
Chromosome karyotype ordered and diagnosis confirmed	10.0 (2 months–30 years)	21.1 (7 months–40 years)	7.6 (2 days–28 years)
Difference in age of first concern to age of diagnosis	4.8 years	2.0 years	5.2 years