SPECIAL REVIEW

A Review of Klinefelter's Syndrome in Children and Adolescents

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Abstract. Klinefelter's syndrome (XXY syndrome) **has been defined as the spectrum of phenotypic features resulting from a sex chromosome complement that includes two or more X chromosomes and one or more Y chromosomes. Cytogenetic surveys conducted across the world have identified a sizable population of XXY males, who have been studied extensively from the newborn period through adolescence.** The longitudinal studies of these boys have produced an accurate and reliable account of the growth and development of the XXY male. There now exists a growing **body of knowledge that suggests that XXY boys often experience language deficits, neuromaturational lag, academic difficulties, and psychological distress, which may be reduced or ameliorated by early identification, anticipatory guidance, and proper medical management. J.** *Am. Acad. Child Adolesc. Psychiarry, 1991, 30, 2: 167-172.* Key **Words:** Klinefelter's syndrome, genetics, sex chromosome anomalies.

Klinefelter's syndrome (47XXY) was first described by Klinefelter et al. (1942) in terms of endocrinological findings. With the advancement of cytogenetics, Klinefelter's syndrome (KS) is now recognized as a sex chromosome anomaly characterized by a surplus of X chromosomes in phenotypic males (Bradbury et al., 1956). The 47XXY complement is the most common chromosomal pattern in persons with KS; however, mosaic patterns (i.e., 46XY/47XXY) and on rare occasions KS variants (i.e., 48, XXXY) are observed. KS is estimated to affect between 1 in 500 and 1 in 1,000 live born males; two-thirds of whom are predominantly of the 47XXY karyotype (Polani, 1967; Hamerton et al., 1975).

Early studies of XXY males produced the disturbing findings of an increased risk for psychiatric disturbance, criminality, and mental retardation (MacLean et al., 1962; Forssman and Hambert, 1963; MacLean et al., 1968; Forssman, 1970; Nielsen, J., 1970; Hook, 1973; Witkin et al., 1976). However, the subjects of early investigations were often found in clinical or institutional settings and had exhibited a degree of pathology that had warranted admission to a mental hospital, prison, or mental/penal institution. The results of early investigations of institutionalized XXY males are considered highly questionable because of selection bias inherent in studies of institutionalized populations and associated problems in research methodology. The more recent studies of XXY boys identified in cytogenetic surveys conducted in eight centers throughout the world have produced reliable information regarding the growth and development of these boys during childhood and adolescence (Leonard et al., 1979, 1982; Nielsen et al., 1979, 1982, 1986; Ratcliffe et al., 1979, 1982b, 1986; Robinson et al., 1979b, 1982, 1986; Stewart et al., 1979, 1982b, 1986; Evansetal., 1982, 1986; Walzeretal., 1982, 1986;Leonard and Sparrow, 1986).

This report will review current knowledge of the genetic and endocrinological characteristics of KS as well as the psychological functioning of XXY males in childhood and adolescence.

Genetic Characteristics

KS is the result of a meiotic nondisjunction during gametogenesis of the egg or sperm. Sanger et al. (1977), in summarizing the data collected in studies of X-linked genes in individuals with sex chromosome abnormalities to determine the parent in which the nondisjunction occurred, reports that in 67% of the males with 47XXY karyotype, the abnormality was due to nondisjunction in the mother. There are no known predisposing factors that have been identified as causative or preventative. Studies have suggested that there is a significant increase in risk for 47XXY live births with advanced maternal age (Carothers and Fillippi, 1988).

Clinical impression can only raise the suspicion of the diagnosis of KS; the phenotype is so variable that the only symptom may be infertility in adulthood. Confirmation of this diagnosis can be achieved through karyotype analysis of peripheral blood or skin fibroblast. The buccal smear should not be used for confirmation but may be a useful screening tool.

Growth and Sexual Developtnent

In summarizing the findings of prospective studies, Robinson et al. (1979a) report an increased incidence of congenital abnormalities among 47XXY infants. Eighteen per: cent of XXY males were found to have one or more congenital abnormalities as compared with one percent of their siblings. Minor congenital anomalies were observed in 26% of the XXY children as compared with 7% of their sibs.

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The mean weight and height of XXY infants falls within the normal range at birth, although significantly lower birth weights have been observed by Ratcliffe et al. (1979) and Stewart et al. (1979) compared with controls and siblings. The head circumference of XXYs tends to be small (Stewart et al., 1982b) and remains so during childhood and adolescence (Ratcliffe et al., 1982a). As the XXY male increases in age, his height is found to be increasingly above normal; height velocity is significantly increased from the age of 5 compared with sibling controls, and there is a significant tendency to have proportionately long legs in childhood (Stewart et al., 1982a). The bone age of XXY boys has been found to be, on an average, two standard deviations below the mean until 8 years of age but approaches the mean at 12 years of age and may advance as much as 3 years within 1 chronological year with the onset of puberty (Stewart et al., 1986).

The sexual development of XXY boys is normal at birth and continues to be normal during prepubertal years; below average testicular volume and stretched penile length are often found in prepuberty but measure within the normal range for age (Stewart et al., 1982b). Ferguson-Smith (1959) reports that the prepubertal testes of XXY boys show a reduced number of germinal cells, and azoospermia is virtually the rule. The XXY adolescent demonstrates a normal progression of puberty at 13 to 15 years of age; however, testicular size increases slowly and remains well below the mean for age (Stewart et al., 1986). After the increase in testicular volume occurring in puberty, testicular growth ceases and later decreases in size (Robinson et al., 1986). The mean testicular volume of XXY adolescents is 3 ml, which is similar to the testicular size (usually less than 3.5 ml [Boisen, 19791) of adult men with KS. Gynecomastia may be a significant problem for some adolescent and adult XXY males (Lancet, 1988).

Neuroendocrine Functioning

The pituitary-gonadal functioning of XXY boys has been found to be normal during childhood; follicle-stimulating hormone (FSH) and luteinizing hormone (LH) values are within the normal range before the onset of puberty (at age 12) but are elevated at the age of 14 (Robinson et al., 1986). A rise in serum testosterone is observed in adolescence, but reaches a plateau after the age of 14 and does not rise above mid-normal range. The XXY boys are clearly hypergonadotropic by the age of 13 to 14 (Stewart et al., 1982b; Robinson et al., 1986). Beginning at puberty, a variety of abnormalities in the hypothalamic-pituitary-testicular axis are seen. Testosterone levels may be normal (Samaan et al., 1979) or low (Ratcliffe et al., 1982a). These levels are maintained by increased hypothalamic secretion of gonadotropin releasing hormone and pituitary secretion of LH and FSH **because** of decreased testosterone feedback on the hypothalamic pituitary axis (Ratcliffe et al., 1982a). The mean plasma LH response to Gn RH stimulation is increased, while the FSH response is diminished (De Behar et al., 1975). The hypersecretion of gonadotropin by the pituitary has been reported to lead to enlargement of the sella turcica (Samaan et al., 1979). There is also increased conversion of testosterone to estradiol (Garbrilove et al., 1980). The increased estradiol to testosterone ratio may account for the increased incidence of gynecomastia seen in patients with KS. Young adult XXY males have been found to have significantly higher LH and FSH and lower concentrations of testosterone compared with controls (Schiavi et al., 1978).

Testosterone Treatment

The success of testosterone treatment in producing improvement in the emotional and behavioral characteristics of XXY males has not been firmly established. Several authors have reported positive effects of testosterone treatment in XXY boys as related to learning and behavior (Annell et al., 1970; Johnson et al., 1970; Caldwell and Smith, 1972; Sorensen et al., 1981). Sorensen and his colleagues (198 1) administered testosterone enanthate 100 mg intramuscularly every third week, and if no effect was found, increased the dosage to 200 mg. Ten of 11 boys treated reported increased vitality, zeal, and concentration ability. In contrast to the findings of Sorensen and his colleagues (1981), Stewart et al. (1986) found treatment of testosterone cypionate, 100 mg every 4 weeks, to have no effect on the behavior, personality, or school performance of XXY boys 13 to 15 years of age. The treatment was successful only in initiating puberty in those boys whose onset of puberty was delayed. Stewart and his colleagues (1986) did, however, suggest that testosterone treatment with more physiological doses of testosterone administered at more frequent intervals might produce beneficial effects on psychosocial adaptation, academic performance, and psychosexual adjustment. Significantly, Nielsen et al. (1988) report that testosterone cypionate and testosterone enanthate induce an increase in serum testosterone level for only 12 to 14 days. Therefore, the 4-week intervals between injections used by Stewart et al. (1986) were considered too long. Accordingly, Nielsen et al. suggest that the lack of significant effect of testosterone treatment found by Stewart et al. (1986) cannot be taken as evidence of lack of effect of testosterone treatment. Nielsen et al.'s (1988) follow-up study of 30 XXY adult males treated with testosterone indicated that 77% of the men were judged to have benefited from testosterone treatment. The men reported more endurance and strength, less fatigue, more activity, better working capacity, improved concentration, better learning ability, better mood, less irritability, less need for sleep, and better relations with others. Nielsen et al. (1988) recommend that testosterone treatment be offered to XXY boys, preferably at the age of 11 to 12 in an effort to promote normal pubertal development and to have a stabilizing effect on emotional development.

Cognitive Development

Intelligence

The diagnosis of KS does not denote a specific level or category of intelligence. Studies of XXY males have identified individuals functioning within the above average to superior range of intelligence (Nielsen et al., 1982; Theilgaard, 1984; Robinson et al., 1986; Walzer et al., 1986). In summarizing prospective studies of XXY's identified at

birth, Stewart et al. (1982a) report that only 18.7% of XXY boys studied had a full-scale IQ below 90; of those identified as having a depressed full-scale IQ, 47.5% had a decreased verbal IQ, which negatively impacted the full-scale score. The global intelligence of XXY boys has appeared below that observed in siblings and controls (Robinson et al., 1979a), but low IQs have mostly been found in the verbal areas; whereas, performance scores have not been found significantly reduced (Nielsen et al., 1979; Evans et al., 1982; Pennington et al., 1982; Stewart et al., 1982b, 1986; Walzer et al., 1982, 1986; Leonard and Sparrow, 1986; Ratcliffe et al., 1986; Netley, 1987; Graham et al., 1988). Decreased verbal IQs have also been observed in XXY adults (Theilgaard et al., 197 1; Porter et al., 1988), which suggests that verbal deficits observed in childhood and adolescence continue into adulthood.

In summary, research findings indicate that XXY males are most often of normal intelligence, may demonstrate a slight deficit in global intelligence compared with controls that appears related to decreased verbal scores, and, overall, demonstrate a wide spectrum of IQ scores.

Language Development

XXY boys frequently demonstrate delayed speech and language development that may be detected as early as 2 to 21/2 years of age (Leonard et al., 1974, 1982; Bancroft et al., 1982). In summarizing the findings of sex chromatin surveys of newborns conducted between 1967 and 1974, Robinson et al. (1979a) report that half of the XXY boys studied demonstrated significantly delayed speech development compared with their siblings. The parents of young XXY boys report delayed speech and language development in their children, with deficits noted in sentence-building skills, speech and production, intonation and accent, or in finding specific words to express thoughts clearly (Walzer et al., 1982). Leonard et al. (1979, 1982) report a significantly decreased developmental rate of language among XXY boys aged 2 to 21/2 years that followed these boys into the school years. These children continued to demonstrate impaired language development at 8 to 9 years of age, exhibiting language deficits in the areas of articulation, comprehension, verbal abstraction, sequencing, and ability to clearly express a story idea.

Graham et al. (1988) find that XXY boys demonstrate impairment in expressive language, which appears related to a pattern of deficits including problems in rate and order processing of auditory stimuli, problems understanding complex grammatical constructions, and problems in oral language. Problems in oral language include deficits in morphology, word-retrieval abilities, and narrative construction. The results of Graham et al.'s study (1988) suggest that XXY boys are handicapped by auditory rate processing difficulties and auditory memory deficits with concomitant difficulties in expressive language. Their expressive language deficits appear to involve difficulties in word finding, syntax production, and narrative formulation.

The language deficits apparent in XXY children are also observed in adults. Theilgaard (1984), in a study of XXY males identified in a birth cohort of tall men in Copenhagen, found XXY adults to have difficulties in articulating and structuring verbal expression. Their weakness in verbalization was demonstrated by a lack of precision, incomplete sentences, vagueness, awkward word-construction, difficulty in word mobilization, and the use of words without a preestablished reference to what the words might designate. Additional evidence that the verbal deficits observed in XXY children may continue into adulthood is provided by Porter and her colleagues (1988); when XXY adults were compared with matched controls, the XXY males demonstrated significantly poor performance on three of four tests used to measure verbal ability. An analysis of WAIS-R Verbal Subtests indicated that none of the men with KS scored beyond the fiftieth percentile on any of the verbal subtests.

Motor Development

Motor development of XXY boys falls within the normal range; however, a tendency to poor gross motor coordination has been observed (Nielsen et al., 1979; Robinson et al., 1979a, 1982, 1986). Robinson et al. (1979b) find XXY boys to be motorially slow and awkward in infancy and early childhood, which is thought to be related to neuromaturational lag. The children studied by Robinson and his colleagues (1979b, 1982) demonstrated delayed neuromaturation. Poor gross and fine motor coordination was observed as well as visual-motor and sensory integration problems, which were manifested in difficulty with eye-hand coordination, distractibility, impulsivity, and short attention span. Balance and equilibrium difficulties were also evident. Interviews with parents of the XXY boys suggested that neuromuscular delays affected school performance in areas associated with writing skills, timed activities, and athletic activities with peers. The neuromaturational lag identified in early childhood is thought to persist well beyond these years by Robinson and his colleagues (1986), who found that their sample of XXY between the ages of 9 and 17 years achieved lower mean scores than controls on tasks involving gross and fine motor skills, coordination, speed and dexterity, and strength.

Educational Performance

The most consistent finding in the investigation of XXY males is that of poor school performance. Stewart et al. (1982a) report that all of the eight centers participating in chromosome surveys and studies of newborns have reported that educational problems are common in their samples (63.7% of the 58 XXY cases as compared with 26.3% of the controls). In summarizing the findings of longitudinal studies of boys with the sex chromosome aneuploidy XXY, Netley (1986) reports that 67.6% of the XXY boys were judged to have educational problems in comparison with 22.2% of matched controls.

Although of normal intelligence, XXY boys demonstrate poor reading and spelling skills (Stewart et al., 1979; Leonard et al., 1982; Ratcliffe et al., 1986; Netley, 1987; Graham et al., 1988). These children have been found to require exceptional education and to repeat a grade at a much greater rate than siblings or controls (Leonard et al., 1979, 1982; Robinson et al., 1982, 1986; and Stewart et al., 1982b,

1986). Reading difficulties are especially noted in XXY boys, with Ratcliffe et al. (1986) reporting that 66.7% of the boys that she and her colleagues studied required remedial teaching in reading. Robinson et al. (1986) reported that 50% of the XXY boys studied by his group appeared to have a specific dyslexia, and 11 of 14 boys had problems in reading.

In an investigation of the oral and written language abilities of XXY boys, Graham et al. (1988) found that these boys had difficulty mastering basic skills of word analysis, and that their problems in word analysis were associated with decreased accuracy and rate of oral reading and reduced comprehension of text-related material. The children's deficits in reading, word analysis, and spelling were found to be associated with the presence of oral language problems and decreased auditory processing abilities. Graham and his colleagues (1988) found that those XXY boys demonstrating language disorders in the preschool years also demonstrated disorders of reading and writing during the school years.

Personality and Behavior

Although no specific personality profile or behavioral pattern typifies the XXY male, common characteristics of temperament have been observed. The XXY boy is often described as introverted and quiet, less assertive, passive, demonstrating lower levels of activity compared with other children, and tending to withdraw from group activities (Nielsen et al., 1979, 1982; Stewart et al., 1982b, 1986). The XXY boy also exhibits immaturity to a significant degree and appears susceptible to anxiety (Nielsen et al., 1979; Stewart et al., 1979; Robinson et al., 1982, 1986).

The self-ratings of XXY adolescents, as studied by Ratcliffe et al. (1982a), find XXY boys rating themselves as more tender minded, apprehensive, and insecure compared with controls. They reported more problems with peer group relationships and less sexual interest in girls. Similar findings were reported in Theilgaard's (1984) study of young adult XXY males. These men rated themselves as more nervous, passive, dependent, and less assertive compared with controls. They also reported having difficulty making social contact with others and were less outgoing socially. They demonstrated less self-acceptance, lower levels of ambition and satisfaction, and decreased sexual libido. Ratcliffe et al. (1982a) and Theilgaard (1984) report lower masculinity scores among XXY males, as measured by the Bern's (1974) sex role inventory and the Thematic Apperception Test, respectively. Ratcliffe and her colleagues suggest that masculine attributes are generally socially desirable, and the significantly lower masculinity score of the XXY adolescent in the study could reflect reduced self-esteem. Theilgaard reports that the XXY males studied lacked a crystallized sense of masculinity and appeared to have difficulty living up to the masculine role. She suggests that the parents, siblings, and peers of XXY boys may fail to respond to these children in a manner which would sharpen their awareness of their male gender.

Discussion

The data provided by longitudinal studies of XXY males identified in cytogenetic surveys of newborns and the controlled studies of noninstitutionalized XXY adults have clarified many of the misconceptions associated with an additional X chromosome. We now know that the diagnosis of KS does not denote an increased likelihood of criminality, psychopathology, or mental retardation. To the contrary, the XXY male is most likely to be of normal intelligence (Stewart et al., 1982a; Theilgaard, 1984) free of psychiatric disturbance (Netley, 1986; Nielsen and Pelsen, 1987), and demostrates no more criminality than observed in XY men when intelligence and parental socioeconomic status are controlled (Schiavi, et al., 1984). There have been, however, deficiencies observed in XXY boys that impact their psychological development. XXY boys commonly exhibit speech and language delays in early childhood that appear predictive of academic difficulties during the school years (Graham et al., 1988). Verbal deficits are frequently observed in XXY boys as measured by the verbal subtests of the Wechsler Preschool and Primary Scale of Intelligence and Wechsler Intelligence Scale for Children-Revised, with a resulting decreased verbal IQ (Nielsen et al., 1979; Stewart et al., 1982a), and it has been reported that verbal deficits continue to be exhibited by XXY adults as measured by the verbal subtests of the WAIS (Porter et al., 1988). The problems XXY males experience in language production, processing, and structuring are thought to interfere not only with the ability to communicate, but also with the acquisition of reading skills and spelling. This has certainly been the case in XXY boys, in that these children demonstrate educational difficulties at a highly significant level especially in the areas of reading and spelling (Stewart et al., 1982a). XXY boys have also been observed to have poor fine and gross motor skills as compared with matched controls that may interfere with school performance in the areas of writing, timed activities, and athletic activities with peers (Robinson et al., 1982, 1986).

The precise relationship between an additional X chromosome and the cognitive development (intelligence, learning, language, and neuromotor skills) of the XXY male is currently speculative. Stewart et al. (1986) postulate that impairments in the cognitive development of XXY males are due to prenatally occurring disturbances in growth. Stewart et al. cite the research of Waber (1977) who found that physical growth and certain cognitive skills are related. She demonstrated that slow maturers are more skilled spatially than verbally; whereas, fast maturers demonstrate the opposite pattern of skills. In keeping with Waber's theory, XXY boys demonstrate delayed bone age maturation and are verbally weak. In further support of the relationship of physical growth and cognitive development, Netley and Rovet (1982) report that individual differences in bone age maturation in XXY males are related to their degree of verbal deficit. Waber (1977) also found that maturation rates influence hemispheric organization, with slow development being associated with a greater left versus right hemisphere asymmetry for verbal processing than fast development. XXY males demonstrate lower than normal degrees of left hemisphere specialization for language and greater than normal degrees of right hemisphere specialization for nonverbal

processing (Netley and Rovet, 1982). Stewart et al. (1986) postulate that slow rates of prenatal growth retard the development of the left hemisphere, which in turn allows the right to develop free of inhibitory influences from the left. The authors suggest that XXY boys with the slower rates of growth are those whose right hemispheres are more functionally active. Stewart and his colleagues (1986) have found that XXY males demonstrating elevated right hemisphere scores also demonstrate the greatest deficit in verbal IQ relative to performance IQ.

In an effort to understand why XXY males experience similar temperament styles and maladjustment, Stewart et al. (1986) studied hormonal functioning, quality of parenting, and hemispheric specialization of adolescent XXY boys. Each of the three factors studied were found to influence temperament and adjustment. Stewart and his colleagues cite the work of Tucker and Williamson (1984) to explain the relationship between hemispheric functioning and social-emotional development. The left hemisphere has been identified as playing a role in controlling tonic activation levels, internally focused serial attentional and motor mechanisms, and motivation. The right hemisphere facilitates habituation to repetitive stimuli, responds to novelty, and is considered important in regulating emotion. Stewart et al. (1986) theorize that the hormonal effects on temperament and adjustment emerge during adolescence and act upon qualities of temperament already influenced by hemispheric organization and environmental factors, such as family functioning.

The combination of poor language skills, academic difficulties, and a tendency to poor fine and gross motor coordination would seem to set the stage for social and psychological difficulties. The child may have poor social skills related to language/verbal deficits (Stewart et al., 1986) and diminished self-esteem related to school failure and impaired motor functioning that interferes with athletic abilities and normal adaptive processes (Robinson et al., 1986). The XXY boy's sense of identity and self-concept may be tested during adolescence as he experiences problems in sexual development that may include gynecomastia and decreased testicular volume (Stewart et al., 1982b, 1986).

The early identification of boys with KS is recommended (Nielsen et al., 1982, 1988) in an effort to provide parents with information and counseling regarding the development of KS, particularly the importance of addressing delays in neuromuscular development, language, and learning at an early age.

The diagnosis of KS should be considered in boys with language difficulties, learning problems, behavioral difficulties, lack of coordination, long limbs with upper to lower segment ratio, increased height, and small penis and testes for their age (Jones, 1988). Testosterone treatment at the age of approximately 12 years is recommended in order to bring about a more normal adolescent development and to possibly serve as a prophylactic against deviations in behavior and learning abilities (Nielsen et al., 1979, 1982; Nielsen and Pelsen, 1987; Nielsen et al., 1988).

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