Mental Development in Polysomy X Klinefelter Syndrome (47,XXY; 48,XXXY): Effects of Incomplete X Inactivation

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ABSTRACT

The child with XXY or a variant form is a fertile ground for scientific investigation because of the homogeneity of the disorder and the increased prevalence of learning disorders associated with it. However, the research studies of boys with XXY (Klinefelter syndrome) have been plagued by a variety of factors from small sample size, methodological flaws, and ascertainment bias. In spite of these shortcomings, there remains some consistency to the neurobehavioral profile of this disorder. In general, the prenatal population of boys with XXY is less affected developmentally and is more academically successful than the boys identified through postnatal diagnosis. Boys with XXY often have decreased muscle tonus, delayed speech, and language skills with an increased incidence of reading differences and dyslexia. It does appear that social difficulties may be mediated by language processing problems and temperamental issues. The neurobehavioral and neurocognitive phenotype of boys with XXY places them at risk for school failure and secondary behavioral disturbances. Therefore, early evaluation and intervention is strongly recommended since the prognosis may be improved significantly with appropriate therapeutic intervention.

The natural history of this disorder is not well defined from the neurodevelopmental, neuroimaging, and cytogenetic perspective. Further investigation into the effects and the relationships between parental origin and outcome may provide many answers regarding the variability of the disorder. Lastly, some promising theories have been postulated regarding the neurobiological etiology of this disorder, which requires more investigation if we are to understand the pathogenesis of this XXY and its effect on learning.

KEYWORDS: Neurodevelopment, XXY, Klinefelter syndrome, cognition

In 1942, Dr. Harry Klinefelter described a small group of men who were different phenotypically with gynecomastia, above average height, and infertility.[1] Shortly after the identification of 46,XY as the typical male complement in 1956, Klinefelter's syndrome was described as XXY, a polysomy disorder. The prevalence of XXY in the general population has been determined through newborn screening in both the United States and Europe.[2–5] The Danish study by Neilsen and Wohlert[3] is the most comprehensive newborn study and determined the prevalence of males with XXY as 1 in 426. In other studies, the prevalence has been estimated

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between 1 in 700 and 1 in 900 live births with the majority of individuals having a 47,XXY chromosomal complement and the variant forms including mosaicism 46,XY/47,XXY and 48,XXXY and 48,XXYY occurring in 20% of male births.[6,7] XXY and variant forms are equally distributed among socioeconomic levels and racial groups.

The prevalence of this disorder suggests that there should be approximately 250,000 males in the United States with XXY. However, the ascertainment of this disorder continues to be decreased, more so in minority populations.[8] There are several typical times of diagnosis for the child with XXY. Most boys are identified during pubescence or early adolescence because of delayed pubertal development, and fertility issues bring adults to the attention of reproductive endocrinologists. However, with technological advances in obstetrical procedures and the passing of Public Law IDEA, increasing numbers of children with XXY have been identified through prenatal diagnosis and at school age when reading differences and behavioral symptoms become apparent to educational personnel and primary care professionals.[9]

Although there are more than 35 published articles on the psychological aspects and learning differences associated with XXY, a comprehensive review of the literature reveals that early neurocognitive studies had small sample sizes, ascertainment bias, and methodological errors. In these older studies, XXY individuals were described as having deviant behaviors with increased prevalence of psychiatric disease. These studies portrayed a poor prognosis for the child with XXY and were flawed with marked ascertainment bias because studies were conducted in penal institutions.[10,11]

More recently, better designed scientific studies demonstrate an improved prognosis for individuals with XXY with normal intelligence, although there is an increased incidence of learning differences and an atypical neurodevelopmental profile discernible by school age.[3,5,12–15] In one study, Samango-Sprouse and Law[16] described developmental differences that were identified within the first year of life in a large sample of children diagnosed prenatally.

NEUROBIOLOGICAL ETIOLOGY OF XXY

Research in learning disorders has always been limited because of the heterogeneity of the children and the variability of their etiologies. It was difficult and often impossible to identify the primary causative factors in many research studies, and conclusions were often flawed by extraneous interfering variables. The field of behavioral neurogenetics, a recent and novel approach, has assisted with the investigation of the relationships between brain and behavior in genetic disorders with associated learning disabilities.[17] The homogeneity of these genetic disorders and the increased prevalence of learning disabilities have enhanced our ability to identify correlations, to draw conclusions, and to formulate inferences regarding the relationship between the neurobiological deficit and the neurodevelopmental performance. It has allowed us to move from "gene to brain to observed manifestations in learning and behavior."[17] In addition, in some chromosomal disorders, it has been demonstrated that parental origin of the chromosome and specific genes has a significant impact on phenotypic expression and subsequent neurodevelopmental outcome of children.[18,19] This could be very critical in XXY because the etiology of the additional X's may further increase our understanding of the disorder as well as explain the variability of the performance of these boys.

Although the neurocognitive aspects of XXY are not well understood, some promising theories have been postulated regarding the etiology of neurodevelopmental differences. Geschwind et al[20] hypothesize that learning differences in individuals with XXY are primarily related to the presence of the additional X. This supplementary material alters the development of the brain and subsequently the learning profile in a specific manner that results in (1) language-based learning disability, (2) increased incidence of dyslexia, and (3) altered cerebral hemispheric dominance.[20]

This theory can be supported by the consistent findings of the decreased verbal abilities (left hemispheric function) with increased spatial cognition (right hemispheric function) in boys with XXY.[21,22] The similarities in deficits in children with XYY and XXX give further credence to the influence of the additional X because there is an increased prevalence of language-based learning problems with reading disabilities in these disorders.[4,22–25]

Further supporting the influence of the X chromosome, girls with XO (Turner's syndrome) usually possess the inverse developmental profile of boys with XXY with decreased spatial abilities and increased language capacities. This strongly suggests that major contributory factors may be the extra X or Y because in the polysomy disorders of XXX, XXY, and XYY, there is only one active X and the additional X or X's undergo inactivation to some extent.[26] Several studies investigating X activation and cognitive functioning have revealed impaired functioning with mental retardation when there is atypical X inactivation in girls with Turner's syndrome.[18,19] Geschwind et al[20] hypothesize that there is an atypical or faulty inactivation of some genes or genetic regions on X or that the genes from the pseudoautosomal regions (PARs) that exist on both X and Y chromosomes are altered and affected by the existence of the polysomy. These hypotheses are tantalizing from a neurodevelopmental perspective for several rea-

sons. A genetic explanation could explain simultaneously the differences between XO and the other sex chromosome anomalies (SCA) disorders as well as the similarities among the three SCA disorders of XXX, XXY, and XYY.

Parental origin and level of skewed X inactivation may be helpful in further elucidating the phenotypic variability present in XXY syndrome. The additional X chromosome is of paternal origin in 50 to 60% of the XXY births with maternal origin occurring in 40 to 50% of the cases.[27,28] A recent study has demonstrated evidence of skewed X inactivation in patients with XXY and the variant form of XXYY.[29] Skewed inactivation may explain the variability in the individual children observed with XXY from no learning issues and only infertility to significant compromise of their well-being because of dosage effect. This study provides preliminary substantiation of the importance of understanding the relationship between parental origin of X inactivation and the phenotypic presentation in individuals with XXY.

An alternative theory for variability in individuals with XXY is the impact of gonadal steroids. This theory hypothesizes that depressed fetal hormones may alter brain development and specifically the development of hemispheric asymmetry in boys with XXY.[30] The theory of atypical brain development could explain the smaller head circumference of boys with XXY because it suggests a delay or slowing of cell division during prenatal development.[31] The atypical cell development retards the maturation of the left hemisphere, and subsequently the right hemisphere matures without the natural biologic influences observed in typically developing children.[24]

Boone-Brawer et al[32] and Robinson et al[33] have demonstrated the evolution of verbal and performance scores in boys with XXY from childhood through adolescence to adulthood. They postulate that the normalization of verbal deficits is a result of the hormonal changes that occur in boys with XXY because of atypical metabolization of testosterone and estradiol. Conversely, there are several valid arguments against a hormonal explanation for the variance in learning in boys with XXY. First, men who are hypogonadal do not have similar neurodevelopmental profiles.[34] Second, both XXX and XYY have very similar neurodevelopmental performance yet have opposite gonadal functions.[4,21,23,24] Finally, boys with XXY have a cognitive phenotype typical of males in spite of the hypoandrogenic profile, which is more feminine from a hormonal perspective.[20] Further formal studies to evaluate the link between all of these factors and their interaction are warranted because the findings will enhance our understanding of the pathogenesis of this disorder and result in more syndrome-specific interventions.

THE INFANT AND TODDLER WITH XXY (KLINEFELTER SYNDROME)

The young child with XXY affords clinician and researchers an excellent opportunity to observe the natural history of learning differences and the evolution of brain-behavior relationships from infancy through adulthood. From a neurocognitive perspective, the infant identified through prenatal diagnosis will have a very different course from a developmental, educational, and medical perspective than the adult diagnosed in the third decade of life. The boy with XXY diagnosed prenatally represents the population of XXY that would not have been ascertained without our technological advances until much later in life, if at all. Because of the prenatal diagnosis, the family made a choice regarding the continuation of the pregnancy after the identification of a chromosomal anomaly. Typically, these families make a conscious commitment to their child and his well-being. Predominantly, the boy with XXY diagnosed prenatally is from a well-educated, middle-class family with the majority of families having at least a college education and many with postgraduate degrees[35] (C. Samango-Sprouse, unpublished data, 1999, 2000). These factors contribute significantly to the well-being of the child as well as to the neurocognitive outcome.[35,36]

The neurobehavioral phenotype of the infant and toddler with XXY has become more distinct with prospective studies of boys identified through comprehensive newborn screening and prenatal diagnosis. An early study by Haka-Ikse et al[37] investigated the developmental achievement of young children with XXY as well as other sex chromosomal abnormalities and documented global but mild developmental delay. Robinson et al[5] conducted a comprehensive newborn study on 40,000 births in Denver and then followed a group with XXY and compared them with typically developing controls. Results indicated delayed ambulation skills (mean age = 18 months) with delayed speech at 24 months of age. Although identification was made through routine newborn screening, the study was conducted in a public hospital with a majority of the births to impoverished or dysfunctional families.[25]

Samango-Sprouse and Law[16] have studied a large cohort of infants with XXY (n = 72) who were identified through prenatal diagnosis. Comprehensive neurodevelopmental assessments were completed over a 5-year period with a 62% incidence of decreased muscle tonus and atypical movement patterns. The Psychomotor Development Index (PDI) was 88.46 (SD12.39) and was significant at P <.001 (C. Samango-Sprouse, unpublished data). The majority of the infants had received some form of early intervention because of at-risk diagnosis or decreased muscle tonus. Speech delay was evident at 12 months of age with decreased phonemic development and difficulty with sound production

in imitation and age-appropriate or advanced receptive language skills (P <.001). Twenty percent of the infants had a "pseudotorticollis" with flattening of the occipital area and decreased range of motion to the contralateral side of the pseudotorticollis. These findings suggest a decrease in motoric activity as early as 2–3 months of age with preferred posturing secondary to truncal hypotonia (C. Samango-Sprouse, in preparation).

From a neurobehavioral perspective, infants with XXY reveal well-modulated alert states with a strong preference for visual stimulation evident within the first months of life (C. Samango-Sprouse, raw data). Hypothetically, the clinical significance of this finding could be related to Giedde's findings of enlarged occipital area on magnetic resonance imaging (MRI) in boys with XXY in comparison with normal controls (J. Giedde et al, unpublished data). This is a tantalizing concept because boys with XXY often have accelerated development in visual-spatial cognition; perhaps this is an early presentation in infancy. Conversely, the infant's preferential response to visual stimuli may be connected to identified auditory processing deficits and reading differences in the older child with XXY,[38] as perhaps these infants are less competent in processing auditory information during infancy. Further investigation is warranted into the correlation between MRI findings and developmental performance in boys with XXY from infancy throughout adulthood. If early differences in brain function can be identified in boys with XXY, then remediation may be more effectively accomplished because of brain plasticity in these early childhood years.

CASE STUDY 1

B is a 3½ year old child with XXY (Klinefelter's syndrome) who was a 7-lb 1-oz product of a 40-week gestation Gravida 1, Para 1, 35-year-old Caucasian female with a normal spontaneous vaginal delivery. He was diagnosed through amniocentesis. This was a highly desired pregnancy for both parents. Family history is negative for any learning disabilities, mental retardation, or physical handicapping conditions on either side of the family. Mrs. B had a master's degree and Mr. B. had a high school education. Disciplinary styles of both parents were child focused with direct consequences for good behavior and time-out for negative behavior. Mr. B and Mrs. B shared child-rearing responsibilities.

Developmental Milestones

At 8 weeks of age, B had a torticollis and decreased muscle tonus. He began physical therapy shortly after the evaluation. B walked at 12 months but continued with difficulty in motor planning until the present time. Speech delay was evident at 12 months of age (Table 1) but receptive language was significantly advanced. He began receiving speech and language services from 12 months (Tables 1 and 2) and he was discharged at 3 years because of above age skills in both expressive and receptive language.

Table 1 B's Neurodevelopmental Performance from Three to Twelve Months

Domain	3 Months	7 Months	12 Months
Gross motor	66	89	88
Fine motor	66	93	100
Receptive language	100	100	119
Expressive language	100	100	81
Cognition	103	106	109
Tonus	Decreased	Decreased	Decreased
Torticollis	Identified	Remains evident	Resolved

At 3 years, he was started in a reading readiness program and is doing well. He reads using both phonetic and sight word approach. His reading comprehension appears quite good. Formal reading battery will be completed between 5 and 6 years of age to assess reading skills. Based on present performance, it is highly unlikely B will have any reading issues. Socially, he was shy but adjusted to preschool with some assistance. He has some playmates and is developing friendships in school. B's level of parental commitment and frequency of early intervention (EI) services are common in boys with XXY who are identified through prenatal diagnosis.

SUMMARY OF STUDIES ON INFANT DEVELOPMENT IN XXY

Although there are few comprehensive studies of infants with XXY, studies have confirmed several pertinent factors from a neurodevelopmental prospective.[21,25,36] Infants with XXY should be evaluated comprehensively within the first 3 to 4 months of life to determine the muscle tonus and status of pseudotorticollis and the need for therapeutic intervention.[36] Because 62% of all infants with XXY have truncal hypotonia, physical ther-

Table 2 B's Neurodevelopmental Performance from Eighteen to Thirty-Three Months

Domain	18 Months	24 Months	33 Months
Gross motor	105	75	114
Fine motor	105	115	115
Receptive language	116	118	140
Expressive language	99	113	133
Cognition	115	142	145
Tonus	Decreased	Decreased	Decreased

apy services may be indicated in the first year of life until independent ambulation and running have been accomplished.[36] Decreased speech skills are evident in the first 24 months of life[39] and possibly as early as 12 months of age.[40] It is advisable to complete a comprehensive speech and language assessment by 18 months of age and determine whether there is a discrepancy between receptive and expressive language development. Although the relationship of these early language findings to later linguistic difficulties has not yet been investigated, it is alluring to theorize that infants with language delay are at increased risk for reading and writing difficulties because research findings indicate that preschool children without chromosomal etiology and speech delays have an 80% chance of later educational problems in the areas of reading and written language (personal communication with Dr. Bonnie Britton, August 29, 2000). With the recognition of significant brain growth during the first 3 years of life and the documentation of the increased learning differences in boys with XXY, early identification and treatment of these variances in infants with XXY are strongly indicated and may prevent later learning differences and secondary behavioral problems.

PRESCHOOL CHILD WITH XXY

Research studies have identified a variety of learning differences in the five neurodevelopmental domains in boys with XXY. From a neurocognitive perspective, IQ is within normal limits but often shifted to the left by 10–15 points from sibling controls.[15,41,42] Decreased verbal ability with evidence of language processing difficulties is evident with language-based learning problems consistently described in 27 different studies.[22] Bone age maturation has been correlated with verbal deficits in boys with XXY.[31]

Language differences are evident within several subdomains in speech and language areas. In toddlers, there is a history of speech delay with later syntactical and grammatical differences observed in preschool years.[39,43,44] Language formulation and word-finding problems were evident in these boys with diminished verbal fluency and memory difficulties.[38,45] Several studies have described deficits in processing, short-term memory, word recall, and phonological development.[21,46] Samango-Sprouse has evaluated 15 preschoolers (age range 36 to 60 months) with sex chromosome abnormalities in the last 3 years. The data were segregated by diagnosis (XXY, XXX, and XYY), although boys with XXY were the majority of the sample. Discrepancy between expressive language skills (SS = 90.00, SD = 10.74) and auditory comprehension (SS = 103.83, SD = 10.01) was significant by 24 months of age. This discrepancy persisted throughout preschool years; however, the children who received intervention appeared to become normal over time. Therefore, boys with XXY had expressive language skills within normal limits of the population controls; however, receptive language skills were often age appropriate to advanced for their chronological age (C. Samango-Sprouse, unpublished data). Fifty-two percent of all children required speech and language services beginning at 18 months and typically lasting through 4 years of age. In Samango-Sprouse's study, short-term recall was mildly deficient for unrelated words but markedly deficient for recall of a short story (unpublished data). These differences suggest either issues of attention to auditory information, short-term memory deficits, or a combination of these two factors. Although data have not been formally analyzed, boys with XXY showed a significant improvement in recall of a short story when visual support was provided (C. Samango-Sprouse, raw data).

MOTOR DEVELOPMENT IN PRESCHOOL YEARS

Early studies of motor development described preschool boys with XXY as clumsy, awkward, and poorly coordinated.[4,39,47] There is one research study that describes the deficiencies in postural control, sensorymotor integration, and motor planning in boys with XXY.[5] Consistent findings of motor planning deficits and organizational issues were evident in Samango-Sprouse's study (unpublished data). When compared with population controls, boys with XXY have deficient unilateral balance regardless of the coexistence of truncal hypotonia. Balance issues were mildly discernible at 24 months of age in boys with XXY; however, at 36 months of age, balance was one standard deviation behind that of peers (C. Samango-Sprouse, raw data). Samango-Sprouse's data revealed atypical motor development in unilateral balance, jumping, and hopping with 68% with truncal hypotonia and 40% appendicular hypotonia. Although truncal hypotonia has not been consistently described in most studies of boys with XXY, symptoms that correlate with decreased muscle tonus have been described, such as delays in walking, clumsiness, neuromaturational delay, and decreased strength.[4,35,39,47]

Balance is believed to be a reflection of cerebellum function and often associated with learning disabilities.[48] Interestingly, several boys with XXY improved in balance skills and intellectual development within 1 year after enrolling in therapeutic intervention (C. Samango-Sprouse, raw data). No causal relationship can be inferred from this observation and the efficiency of therapeutic intervention in general has not been well documented to date.[48] Yet, the basis of this therapy is attention, repetition, planning, balance, and strengthening. The improvement in intellectual development may be unrelated and part of natural maturation. The relationship between learning, muscle tonus, and move-

ment in boys with XXY needs further investigation because this constellation of disturbances is common in XXY and in children with learning problems. Greater understanding of these parameters may enhance our understanding of brain and behavior relationships in children with developmental disabilities.

SCHOOL-AGE CHILD WITH XXY

Research studies on the school-age child have several consistent findings. Intellectual development remains consistently within normal limits but lower than that of sibling controls.[2,4,21] Boys with mosaicism XXY demonstrate the least effect of the aneuploidy on intellectual development with a mean IQ of 117.[2] In Samango-Sprouse's study,[36] the school-age child with mosaicism XXY fit this profile with an IQ of 126, which was one standard deviation below that of his two older siblings. He qualified for a talented and gifted program in school. He had extensive intervention in preschool years to address mild deficits.

Studies reveal slow processing, inattention, and language dysfunction.[3,15,38,49] These boys perform lower in standardized achievement tests, but this is not uncommon with language-based learning difficulties. Mandoki et al[49] and Geschwind et al[20] both discuss the significant impact of language skills on reading comprehension and spelling, which are primary components of dyslexia. Bender et al[21] demonstrated consistent errors in Trail Making Tests, suggesting frontal lobe dysfunction. Boone et al[32] revealed findings consistent with frontal lobe dysfunction in adolescents and adults with XXY. Samango-Sprouse (unpublished data) analyzed data from a small sample of 20 subjects who scored under 8 on the Wechsler Preschool and Primary Scale of Intelligence. Individual analysis of subtests revealed the lowest score consistently on the Maze subtest, which is believed to be an assessment of frontal lobe function. Giedde et al (unpublished data) reported that volume in the frontal area of the brain was significantly smaller in boys with XXY, and Patwardhan et al[50] also reported decreased volume in the temporal area in adults with XXY. Sensory integration issues, attention dysfunction, and mood dysregulation have been reported as well, which are highly related to frontal lobe function.[15,20,32,41,51]

Attention issues with impulsivity have been described in several research studies.[20,31,32] This is a complex issue to discuss because attention issues are commonly seen in children with language disabilities.[52] Although no formal studies have been undertaken, boys with XXY appear to have difficulty with attention in school settings based on anecdotal information such as parental reports and review of school records. Because a primary component of elementary school learning is processing auditory information, it is possible that auditory processing deficits described by Graham et al[38] and others[12,43,44,47] may be a significant contributing factor to the attention issues. Further study in the area of attention and language processing is warranted prior to any conclusion regarding boys with XXY and attention deficit hyperactivity disorder.

TEMPERAMENT IN BOYS WITH XXY

Temperamentally, boys with XXY have been described as quiet, passive, and quite placid primarily in case reports.[24,47,53] There is only one study using the Carey Infant Temperament Scales, but sample size was quite small and there were no control groups of similar age with learning differences.[46] Temperamental differences may be present in XXY because decreased activity and placidity have been described in other chromosomal disorders such as Prader-Willi or Down syndrome.[54] These temperamental differences may be attributed to XXY or to a subset of the boys with XXY with a specific neurocognitive learning profile. Preliminary data of Samango-Sprouse suggest that placidity and activity levels may be highly correlated with the presence of hypotonia and motor and cognitive development (C. Samango-Sprouse, unpublished data). These two factors would also be consistent with previous studies of children with chromosomal disorders and probably are a reflection of brain development as much as temperamental characteristics. Mood regulation, activity, and rhythmicity are some of the components related to frontal lobe assessment and function in the children[36] and therefore early temperamental differences may be a window on the functioning of frontal lobe in later years. Further investigation of familial temperament style, birth order, and parental expectations in conjunction with muscle tonus and cognitive functioning is warranted to determine the temperamental style of infants with XXY in comparison with siblings and its relationship to frontal lobe function in this disorder.

CASE STUDY 2

J is presently an eight-year-old boy with XXY who has had a complex developmental history exacerbated by a conflicted, at times hostile, situation between his parents. J was referred at 6 years 8 months because of school difficulties and was brought to the evaluation by his mother. He lived primarily with his father and girlfriend although custody was shared between his parents. J had an uncomplicated pregnancy and delivery and was diagnosed though prenatal diagnosis. He received some EI services as a toddler and preschooler. His speech was very delayed and he was not understandable until he was 5 years old.

Mrs. X had a high school degree and negative family history for any learning disorder. Mr. X had a high

school degree, worked in auto repair, and was suspected of having a learning disability by his own report. Mr. X believes in corporal punishment with J and often inflicted severe consequences for J's misbehavior. By report, J was often threatened, "He would be sent to jail if he was bad." Mrs. X was a quiet, soft-spoken woman who was more effective with J, but appeared intimidated by her husband's aggression and extremely controlling style.

J had the characteristic learning profile with VIQ of 78 and a PIQ of 118 but more significantly impaired than many boys with XXY (Table 3). He had significant anxiety particularly about his father "hitting him when he is bad." J has been attending a regular classroom but has been "placed in time-out" repeatedly for aggression, impulsivity and, inattention. At 7 years of age, he was placed in a classroom for children with emotionally impairment but continued to have behavioral problems. He was physically restrained several times in school for outbursts. Recently, he was admitted for the second time to an inpatient pediatric psychiatry unit because of a threatened suicide. Medication has largely been unsuccessful for managing his behavior. Several diagnoses have been postulated from ADHD to bipolar to possible schizophrenia. Mr. X has had chromosomal analysis repeated twice because he does not believe that J has XXY. With the last hospitalization, J was restrained in bed, developed enuresis, and had recurrent outbursts, saying "I am a bad boy" over and over in his mother's presence.

J's profile represents the extreme vulnerability of boys with XXY to dysfunctional family situation. He continues to regress in development. J's instability in his home life, conflict between child rearing styles of mother and father, and significant language based learning disabilities put him at great risk in the present and more so in the future. Both parents have now agreed J needs a residential placement for his problems and he awaits an opening in an appropriate residential placement.

MOTOR DEVELOPMENT IN SCHOOL-AGE BOYS WITH XXY

Boys with XXY are particularly challenged by school age in the motor development area. Many aspects of peer relationships and social interactions for elementary-age boys and girls are centered on the playground. Although research studies in this area are scant, there are consistent findings of motoric awkwardness and avoidance of team sports such as soccer or baseball for boys with XXY.[2,49] Samango-Sprouse[36] found that the majority of boys with XXY were delayed in riding a two-wheel bicycle, hopping, and skipping. These skills could be attained closer to normal limits when specific activities addressed the skills acquisition, but often the boys became more avoidant as they grew older (C. Samango-Sprouse, unpublished data). Boys who were enrolled in team sports such as soccer by 5 or 6 years of age were more successful and able to play these sports throughout elementary years. Although these boys may need some assistance with coordination, they enjoy the sports and develop friendships through these activities. Initiation of novel team sports participation becomes increasingly problematic for these boys with age. Individual sports, such as swimming, tennis, and golf, are less stressful for these boys as they mature and are highly recommended to build muscle strength and endurance.[2,49]

Table 3 J's Neurodevelopmental Performance at 80 Months of Age

Gross motor	100
Fine motor	97
Receptive vocabulary	113
Expressive vocabulary	74
Cognition	Performance intelligence quotient = 118
	Verbal intelligence quotient = 78

CASE STUDY 3

M was diagnosed with mosaic XXY (45X/46XY/47XXY) through prenatal diagnosis. It was believed to represent a trophoblast mosaicism. He was the 9-lb product of a full term gestation with a normal spontaneous vaginal delivery to a 38-year-old, Gravida 3, Para 3, Caucasian female and her 38-year-old mate. Pregnancy was complicated by gestational diabetes diagnosed in the second trimester and treated with dietary management. Family history revealed that Mrs. H had a college degree and Mr. H had an MBA. M had two older siblings who were in talented and gifted programs.

Developmentally, M had normal acquisition of speech, language, and motor milestones until two years of age when mild speech differences were noted. Mild truncal hypotonia (Table 4) was documented at 12 months of age and persisted throughout 8 years of age.

Table 4 M's Neurodevelopmental Performance from Infancy through School Age

Domains	12 Months	26 Months	51 Months	96 Months
Gross motor	100	92.30	83	100
Fine motor	100	92.30	103	120
Receptive language	100	109	113	100
Expressive language	100	103	97	100
Cognitive	103	111	117	126
Muscle tonus	Decreased	Decreased	Decreased	Normal

M's sensory motor function was evaluated at 32 months revealing deficient postural control and borderline function in bilateral motor integration. Physical therapy and occupational therapy were given weekly for motor deficiencies between 32 and 60 months of age.

Developmental assessment revealed a consistent profile for the diagnosis of XXY, but deficiencies were mild and responded well to treatment intervention. M demonstrated advanced five motor and receptive language skills by 5 years of age. Cognitive capacity was above average with an IQ of 126 by 8 years of age. At third grade, he tested into gifted and talented programs as his two siblings had previously done into the same program. Both siblings had been evaluated at the 99% whereas M had assessed at the 85% and 90%, respectively, for language and nonverbal skills.

Although reading assessment was not completed, M appeared to have no reading difficulties by report. He was in a regular classroom, had all A's and B's in school, and was reading at least one book a week for entertainment at 8 years of age. Socially, he had friends at school and in the neighborhood. His mother reported that he was easy going, but he "worried" more than her older children. However, this behavior did not interfere with family functioning. Vocabulary was within normal limits but two standard deviations below his cognitive capabilities, yet written language was not affected in school and he enjoyed writing, by report.

M had a neurodevelopmental profile consistent with boys with mosiacism XXY. All developmental disruptions were mild and resolved or presented no significant impairment to his learning or education. He had truncal hypotonia with atypical motor development for several years. In testing, language skills were significantly discrepant from intellectual abilities but did not appear to effect school performance. Functionally, M was a well adjusted, easy going young boy with XXY (mosiac form) in a gifted and talented program in his neighborhood school with minimal differences from his siblings.

VARIANT FORMS OF XXY AND NEURODEVELOPMENTAL PERFORMANCE

The variant form of XXY arises when an extra X occurs in addition to XXY aneuploidy resulting in either 48,XY (XXXY) or 49,XY (XXXXY). There have been only 50 reported cases of XXXY since the original description of this disorder in 1959.[55] Boys with this disorder have more dysmorphic features than boys with XXY as well as structural abnormalities such as genital and occasionally cardiac anomalies.[55] Phenotypically, the boys with 48,XY resemble those with 47,XY with increased stature, long limbs, slender body build, eunuchoid habitus, and increased likelihood of developing gynecomastia.[55] Twenty-five percent of the boys have hypoplasia of the penis, which often brings them to the attention of medical personnel and eventual diagnosis. These boys require hormonal replacement therapy usually in early adolescence, similar to the boys with XXY.

Our knowledge of the neurocognitive phenotype of the variant forms is quite limited because these disorders are rare in occurrence (1:50,000) and usually ascertained from hospitals or residential facilities.[56] The typical IQ of a child with 48,XY is in the subnormal range with mental retardation occurring. The range of reported IQ can be wide but characteristically is from 40 to 60. However, the assessment of mental capacities can be quite challenging because the language impairment is similar in constellation to that with XXY but much more severe.[40,56] Expressive communication can be very problematic throughout preschool years, and some children with the variant forms of XXY may never develop functional speech.[56] Temperamentally, boys with 48,XY are described as pleasant and passive; however, aggressive outbursts occur as a result of frustration and mental deficiencies. Motor development is significantly delayed with motor clumsiness as the child becomes older.[56]

In a small study by Samango-Sprouse and Law,[40] five children who were diagnosed with variant forms of sex chromosome disorders including three with 49,XY, one with 48,XY, and one with 49,XXX had a mean age of 47.4 months and a range from 28 months to 66 months. Parents were from the middle class with several families having college or postgraduate education. All children were comprehensively evaluated in all five developmental domains and showed developmental delay but were significantly higher in function than previously reported except in motor development. Mean IQ was 77.3 (SD = 17.4) with receptive language scores of 77.5 (SD = 10.1) and expressive language scores of 79.4 (SD = 16.8). The most significant delay was in motor development with a mean PDI (Psychomotor Index) of 64 (SD = 12.5). Motor delay in this group was often secondary to the presence of abnormal muscle tonus, usually hypertonia rather than the hypotonia that has been described in XXY.[40] Children had received aggressive multidisciplinary early intervention services including orthotics to assist with walking and sign language to facilitate expressive communication. This is a small study but does suggest that the prognosis for children with variant forms may be improved if diagnosed early and treated aggressively. The intellectual functioning in this group was borderline or low normal, but further intellectual assessment will be necessary as the children mature in order to evaluate the stability of these findings.

There have been 100 reported cases worldwide with the chromosomal complement of 49,XY since the first case was identified in 1960. The incidence is estimated as 1:85,000 to 1:100,000 and the individuals are similarly but more severely affected than those with XXY. Physical features include a variety of anomalies not commonly associated with 47,XY such as cleft palate, cardiac defects (15 to 20%), and short stature. Genitalia are atypical with hypoplasia and cryptorchidism.[55] There is global delay with language impair-

ment. The mean IQ is very similar to that of the children with 48,XY.

SUMMARY OF NEUROBEHAVIORAL PHENOTYPE IN XXY (KLINEFELTER SYNDROME)

Although research studies have been plagued by a variety of factors (small sample size, methodological flaws, etc.), there is a consistency to the neurobehavioral profile of this disorder. In general, the prenatal population of boys with XXY is less affected developmentally and more academically successful than the boys identified postnatally. There are a number of reasons that may explain this phenomenon. Parental education and environment are usually enriched with exposure to the variety of educational materials and appropriately stimulating experiences when the child is identified through prenatal diagnosis.[2,3,57] Parents often obtain intervention services early and aggressively because of the diagnosis.

Boys with XXY have decreased muscle tonus, delayed speech and language skills, and an increased incidence of reading differences and dyslexia. The etiology of this language-based learning disability is not well understood, although two theories have been postulated. There has been little research on the social aspects of language in boys with XXY. It does appear that social difficulties may be mediated by language processing problems and perhaps temperamental issues. The neurobehavioral and neurocognitive phenotype of boys with XXY places them at risk for school failure and secondary behavioral disturbances. Therefore, early evaluation and intervention is strongly recommended because the prognosis may be improved with appropriate therapeutic intervention.

RESEARCH ISSUES FOR THE FUTURE

The child with XXY or a variant form is fertile ground for scientific investigation because of the homogeneity of the disorder and the increased prevalence of learning disorders associated with it. The natural history of this disorder is not well defined from a neurodevelopmental, neuroimaging, and cytogenetic perspective. Further investigation into the effects and the relationships between parental origin and outcome may provide many answers regarding the variability of the disorder. Lastly, some promising theories have been postulated regarding the neurobiological etiology that require more investigation if we are to understand the pathogenesis of this XXY and its effect on learning.

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