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Cognitive and Motor Development During Childhood in Boys With Klinefelter Syndrome

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The goal of this study was to expand the description of the cognitive development phenotype in boys with Klinefelter syndrome (47,XXY). We tested neuropsychological measures of memory, attention, visual-spatial abilities, visual-motor skills, and language. We examined the influence of age, handedness, genetic aspects (parental origin of the extra X chromosome, CAG_n repeat length, and pattern of X inactivation), and previous testosterone treatment on cognition. We studied 50 boys with KS (4.1–17.8 years). There was a significant increase in left-handedness ($P = 0.002$). Specific language, academic, attentional, and motor abilities tended to be impaired. In the language domain, there was relative sparing of vocabulary and meaningful language understanding abilities but impairment of higher level linguistic competence. KS boys demonstrated an array of motor difficulties, especially in strength and running speed. Deficits in the ability to sustain attention without impulsivity were present in the younger boys. Neither genetic factors examined nor previous testosterone treatment accounted for variation in the cognitive phenotype in KS. The cognitive results from this large KS cohort may be related to atypical brain lateralization and have important diagnostic and psychoeducational implications. The difficulty in complex language processing, impaired attention and motor function in boys with KS may be missed. It is critical that boys with KS are provided with appropriate educational support that targets their learning challenges in school in addition to modifications that address their particular learning style. These findings would also be an important component of counseling clinicians and families about this disorder.
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INTRODUCTION

In 1942, Klinefelter et al. described a disorder of testicular failure now called Klinefelter's syndrome (KS) [Klinefelter et al., 1942]. KS is due to a supernumerary X chromosome in males [Bradbury et al., 1956]. About 80% of males with KS have the karyotype 47,XXY, while the remaining 20% have 47,XXY/46,XY mosaicism or higher grade aneuploidy of the X chromosome [Visootsak et al., 2001]. KS is the most common sex chromosome disorder [MacLean et al., 1961; Robinson et al., 1986; Rovet et al., 1995], occurring in 1/426–1/1,000 males [Jacobs, 1979; Nielsen and Wohlert, 1990; Visootsak et al., 2001; Bojesen et al., 2003]. The KS phenotype includes childhood onset testicular failure, tall stature, and characteristic cognitive attributes. Diagnosis is often delayed until pubertal delay or hypogonadism are noted. The defining clinical and

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cognitive characteristics may show substantial variation [Smyth, 1999; Cherrier et al., 2002] and are unrecognized in a substantial fraction of boys with KS.

KS has been reported to be a common cause of developmental delay of unknown cause among prepubertal boys [Khalifa and Struthers, 2002]. Global intelligence (Full Scale IQ), is generally within normal limits, but tends to be less than that of sibs or control males [Robinson et al., 1986; Walzer et al., 1990; Rovet et al., 1995; Ratcliffe, 1999]. Depressed Verbal IQ relative to Performance IQ has been observed in KS children and adults [Ratcliffe et al., 1986; Robinson et al., 1986; Graham et al., 1988; Porter et al., 1988; Walzer et al., 1990; Rovet et al., 1996], although the profile may vary across the life span. This may be accompanied by moderate to severe problems with reading, spelling, writing, and arithmetic [Nielsen et al., 1980; Stewart et al., 1982; Leonard and Sparrow, 1986; Walzer et al., 1990].

Language and speech impairments remain evident in some form at all ages. Significant impairments are frequently observed in higher order aspects of expressive language, particularly in deficits with word retrieval, expressive grammar, verbal processing speed, and executive abilities [Graham et al., 1988; Porter et al., 1988; Walzer et al., 1990; Bender et al., 1993; Ratcliffe, 1999; Geschwind et al., 2000; Boone et al., 2001].

The pathogenesis of the cognitive deficits observed in KS may be developmental, hormonal (testosterone deficiency), or both. Other potential influences also include anomalous cerebral dominance and left hemisphere dysfunction in KS, as reflected in increased left-handedness. Delayed pubertal development and increasing relative androgen deficiency could result in age-related changes in the cognitive phenotype. Genetic influences such as the parental origin of the supernumerary X chromosome, the androgen receptor (AR) CAG_n repeat length and the pattern of X chromosome inactivation could be related to variability of the cognitive phenotype.

Previous studies have examined specific aspects of cognition in KS such as language, but most have included only 10–20 subjects. In this study, we evaluated verbal and non-verbal ability in 50 genetically well-characterized boys with KS, age 4–17 years. We investigated functional correlates of cerebral dominance by evaluating handedness and dichotic listening as well as the influence of genetic factors on cognition in KS.

METHODS

Subjects

Subjects were generally referred to the pediatric endocrinology clinic at Thomas Jefferson University. All had postnatal karyotypes confirming the diagnosis of KS. The study was approved by the Human Studies Committee at Thomas Jefferson University and UT Southwestern Medical School. All subjects and their parents gave informed consent and assent. The clinical evaluation was performed at Thomas Jefferson University and the karyotyping and genetic studies were performed at UT Southwestern Medical School.

Test Procedures

Subjects were individually administered a battery of neuropsychological tests specifically designed to assess memory, attention, visual-spatial abilities, visual-motor skills, and language. The evaluation was administered by trained and experienced psychometricians under the supervision of a licensed neuropsychologist. Raw scores were converted to standard scores (mean of 100, standard deviation of 15), based on the test-specific norms or our own population of age-matched control children.

We chose the Differential Ability Scales (DAS) [Elliott, 1983], to assess general cognitive ability in children ages 4–17 years, 11 months. The DAS cognitive battery includes three composite scores: the Verbal Cluster (VC) score measures semantic knowledge, verbal expression, and verbal comprehension, the Spatial Cluster (SC) score measures nonverbal spatial cognitive ability, and the Nonverbal Reasoning Cluster (NVC) score measures non-verbal aspects of fluid reasoning. Performance on subtests were combined to yield a General Conceptual Ability (GCA) score, which is a general index of an individual's ability to perform complex mental processing involving conceptualization and manipulation of information.

Academic achievement was assessed with the reading, spelling, and arithmetic subtests from the Wide Range Achievement Test-3 (WRAT3) [Wilkinson, 1993]. The tasks used to assess attention/executive function included Conners' Continuous Performance Test (CPT-II, age-specific norms, ages 5–18 years) [Conners et al., 2000], Conners' Kiddie CPT (age-specific norms, ages 4–5 years) [Conners et al., 2000], the NEPSY: A Developmental Neuropsychological Assessment—Verbal Fluency subtest (age-specific norms, 3–7 years) [Korkman et al., 1998], and the Delis–Kaplin Executive Function System (D-KEFS) Color-Word Interference Test (age-specific norms, ages 8–18 years) [Delis et al., 2001]. These tasks measure processing speed, sustained attention, response inhibition, and inhibitory control. We examined aspects of verbal memory using the Children's Memory Scale (CMS, age-specific norms, ages 5–16 years) [Cohen, 1997] for Story Recall and Digit Span [Cohen, 1997], and California Verbal Learning Test-Children's Version (CVLT-C, age-specific norms, ages 5–16 and CVLT-II, age-specific norms, ages 17–18 years) [Delis et al., 1994]. We

assessed visual-motor and visual memory with the Rey–Osterrieth Complex Figure—Copy and Organization scores (age-specific norms, ages 7–60 years) [Waber and Holmes, 1985] and the Beery Test of Visual Motor Integration (age-specific norms, ages 2–17 years) [Beery, 1997].

Language ability was evaluated at the level of single words with the Expressive One-Word Picture Vocabulary Test (EOWPVT, age-specific norms, ages 2–18 years) [Williams, 1997] and the Receptive One-Word Picture Vocabulary Test (ROWPVT, age-specific norms, ages 2–18 years) [Brownell, 2000]. Phonological processing was assessed with the Comprehensive Test of Phonological Processing (CTOPP, age-specific norms, ages 5–24 years) [Rashotte et al., 1999], and fluency with the Delis–Kaplin Executive Function system (D-KEFS) subtest (see above for age norms), which tapped both phonemic and semantic fluency [Korkman et al., 1998]. We evaluated more complex levels of language processing with the Test of Language Competence—Expanded Edition (TLC-E, age-specific norms, ages 5–18 years) [Wiig and Secord, 1989].

The tasks used to assess fine and gross motor skills included the Lafayette Pegboard (age-specific norms, ages 4–18 years) [Klove, 1963], the Bruininks–Oseretsky Test of Motor Proficiency (BOT, age-specific norms, ages 5–14 years) [Bruininks, 1978] and Physical and Neurological Evaluation for Soft Signs (PANESS, age-specific norms, ages 4–18 years) [Close, 1976].

Socioeconomic Status (SES). SES estimate was calculated for children using the Hollingshead 2-Factor Index of Social Status based on education and occupation of parents [Hollingshead and Redlich, 1958].

Handedness and Lateralization. The Crovitz Laterality battery was administered to document hand preferences [Crovitz and Ziner, 1962]. Children were asked to demonstrate which hand they use for eight activities (right hand = RH and left hand = LH). A laterality quotient was calculated using the following formula: $((RH - LH)/(RH + LH) \times 100)$. Right-handedness was defined as a score = 100% (performance of 8 of 8 tasks with the right hand). Non-right-hand dominance was characterized as a score <100% [Kimura and Vanderwolf, 1970]. This is similar to previously reported definitions of handedness [Spreen, 1991; Isaacs et al., 2006].

The Dichotic Listening task was administered to determine lateralization for language processing [Hayden, 1978]. Subjects heard different words simultaneously in both ears and reported which word they heard. The laterality index was calculated with the formula: number correct for right ear minus number correct for left ear, divided by sum of number correct for right and left ear. Right ear preference was defined as preference score >0 [Hayden, 1978].

Genetic Testing

Karyotype. A postnatal G-banded peripheral blood karyotype was obtained for all subjects. Each karyotype counted at least 20 cells.

Parental Origin. Parental origin of the supernumerary X chromosome was determined by genotyping patients and parents with a panel of seven highly polymorphic microsatellite markers distributed along the length of the chromosome as reported previously [Zinn et al., 2005].

X Inactivation Ratio and AR CAG_n Repeat Length. Skewing of X chromosome inactivation was measured using the AR methylation assay as previously reported [Zinn et al., 2005]. The fraction of each X allele that was active (unmethylated) was determined from the ratio of peak areas in the *Hpa*II-digested samples, after correcting for unequal amplification of alleles in the mock-digested samples as described [Zitzmann et al., 2004]. Preferential inactivation of one allele > 80% was considered skewed [Plenge et al., 2002]. The CAG_n repeat length of AR alleles was determined by comparing the mobility of the PCR products used in the X inactivation assay on capillary gel electrophoresis to standards with known repeat lengths determined by DNA sequencing.

Statistics

In this descriptive study, all statistical tests and *P*-values represent descriptive results. All results are presented as the mean ± SD of standard scores. Statistical comparisons included the Chi-squared test and Analysis of Variance (ANOVA). ANOVAs were performed according to (1) age 4.0–9.9 (younger) versus 10.0–17.9 (older) years, (2) maternal versus paternal origin of the extra X, (3) number of AR CAG repeats ≤21 versus >21, and pattern of X-inactivation: random (<0.8), skewed (0.8–0.9), or highly skewed (>0.9). We also compared boys treated versus not treated with testosterone. *P*-values and statistical tests are presented for all comparisons.

RESULTS

Demographics

Our study included 50 boys, ages 4.1–17.8 years. The mean age was 10.6 ± 3.6 years. The mean socioeconomic score was 51 ± 10 (middle class). The sample included 48 Caucasians and 2 African-Americans. Thirty boys had received the diagnosis of KS prior to age 2 (28 for prenatal screening [advanced maternal age], 1 for hypotonia, 1 for small genitalia). Twelve boys were diagnosed at ages 2–12 years (one for tall stature, five because of behavior issues, one for hypotonia, three for language issues, and two at the mother's request), and eight boys were diagnosed after age 12 (two for behavior issues and six for

small testes). Of the 50 boys, 22 were receiving some special education services in school, 26 were in regular classes, and 2 had not yet started school. Forty-two boys received speech and/or reading therapy and 23 received occupational and/or physical therapy by the time of the evaluation.

Two boys (ages 6.5 and 7.8 years, prenatally diagnosed) had received testosterone in infancy for durations of ≤3 months (for treatment of small genitalia or reduced testosterone levels). Nine boys, >14 years, had received testosterone treatment during adolescence (duration of 0.1–2.0 years).

Genetic Results

Karyotype results were: 47 boys with 47,XXY, 1 mosaic 46,XY/47,XXY, and 2 48,XXYY. The parental origin of the extra X chromosome was determined for the 47,XXY subjects; in 30 the extra X chromosome was maternal and in 17 it was paternal. Parental samples were unavailable on the other three boys. The polymorphic AR CAG_n repeat length was measured on 46 of the boys. The range was 16–26 copies, which was within normal limits (11–35) [Kuhlenbaumer et al., 2001]. The median CAG_n repeat number was 21; 23 had CAG_n repeat ≤21 and 23 had CAG_n repeat >21.

X-inactivation ratio was determined in 30 boys; 16 boys had homozygous alleles where the inactivation ratio could not be determined. A total of 26 had random X inactivation (<0.8), 2 had skewed inactivation (0.8–0.9), and 2 had highly skewed X inactivation (>0.9).

Lateralization and Handedness

Based on the Crovitz Handedness Questionnaire, 66% (33/50) were completely right-handed (laterality index of 100%). This was a significant increase in non-right-handedness when compared to the general population: 37% versus 14% [Loo, 1979] ($P = 0.002$, Chi-squared).

On dichotic listening, 54% (20/37) had a right ear advantage (defined as preference score >0), 5% (2/37) had equal findings in both ears, and 41% (15/37) had a left ear advantage. The mean total correct for both ears for the group was 24.0 ± 10.1, which is less than what has been reported in normal males, ages 4–14 years (35.2–52.9) [Spreen, 1998]. The mean lateralization index was 0.08 ± 0.35, also less than indices reported in normal males, ages 4–14 years (0.09–0.39) [Spreen, 1998].

Cognitive Results

Results from the DAS are depicted in Table I, age divided into two age groups: younger (prepubertal, age <10 years) and older (pubertal, age ≥10 years). On the GCA index, the mean Verbal Cluster and Nonverbal Reasoning Cluster scores were less than the Spatial Cluster scores. Performance for GCA was slightly better in the younger, compared to the older group ($P = 0.04$).

Subtest analysis revealed that the younger group had scores within the average range for all subtests, with relative strength on the non-verbal reasoning subtests (i.e., Matrices and Sequential and Quantitative Reasoning) and the spatial subtests (i.e., Recall of Designs and Pattern Construction), in comparison to the Verbal Cluster subtests (i.e., Word Definitions and Similarities). The older subjects had mean performances on subtests that fell within the Low Average range, with the exception of average range scores on the Spatial Cluster (Pattern Construction and Recall of Designs). Performance on the Matrices subtest was better in the younger group than in the older group ($P = 0.02$).

According to the analysis of AR CAG_n repeat polymorphism, the group with greater than average

TABLE I. General Cognitive Ability and Achievement Results (Mean Standard Score ± SD)

	n	Young (<10)	n	Old (≥10.0)	n	Group	*P*-value[a]
DAS index[b]							
Verbal Cluster (VC)	25	90.6 ± 16.1	25	84.4 ± 11.8	50	87.5 ± 14.3	0.13
Nonverbal Cluster (NVC)	26	90.9 ± 22.6	24	84.6 ± 12.2	50	87.8 ± 18.4	0.23
Spatial Cluster (SC)	21	95.3 ± 14.6	25	89.3 ± 13.5	46	92.0 ± 14.2	0.15
General Conceptual Ability (GCA)	24	92.2 ± 14.8	25	84.0 ± 11.4	49	88.0 ± 13.7	0.04
DAS subtests							
Word Definitions	21	90.5 ± 15.3	25	87.3 ± 11.9	46	88.8 ± 13.5	0.43
Similarities	22	90.3 ± 17.0	25	86.5 ± 12.2	47	88.3 ± 14.6	0.39
Matrices	22	97.2 ± 14.0	24	86.6 ± 14.4	46	91.7 ± 15.1	0.02
Sequential and Quantitative Reasoning	22	94.8 ± 14.0	25	88.0 ± 14.0	47	91.2 ± 14.3	0.1
Recall of Designs	21	94.0 ± 15.2	25	90.0 ± 15.8	46	91.8 ± 15.5	0.38
Pattern Construction	26	95.7 ± 17.2	24	91.8 ± 13.1	50	93.8 ± 15.3	0.38
WRAT-3 subtest[b]							
Reading	24	97.4 ± 16.3	25	93.9 ± 14.6	49	95.6 ± 15.4	0.43
Spelling	24	92.4 ± 12.6	25	92.3 ± 12.5	49	92.3 ± 12.4	0.98
Arithmetic	24	89.2 ± 16.6	25	88.8 ± 15.4	49	89.0 ± 15.8	0.94

[a]ANOVA by age.
[b]Age-specific norms.

number of repeats (>21) had better performance on the Spatial Cluster (97.6 ± 11.6, n = 20 vs. 87.7 ± 14.6, n = 26, $P = 0.02$), related in part to significantly higher scores on the Pattern Construction subtest (101.4 ± 13.2, n = 22 vs. 88.0 ± 14.3, n = 29, $P = 0.001$). Performance was slightly better in the right-handed group (lateralization index >50%) compared to the non-right-handed group for GCA (89.9 ± 13.5, n = 42 vs. 76.7 ± 9.2, n = 7, $P = 0.02$), Verbal Cluster (89.5 ± 14.2, n = 42 vs. 77.1 ± 10.6, n = 8, $P = 0.02$), Spatial Cluster (94.3 ± 14.1, n = 38, vs. 81.4 ± 8.7, n = 8, $P = 0.02$), DAS-Word Definitions (90.8 ± 13.4, n = 38, vs. 79.2 ± 9.4, n = 8, $P = 0.03$) and the DAS-Sequential and Quantitative Reasoning subtest (93.3 ± 14.8, n = 38, vs. 82.2 ± 6.6, n = 9, $P = 0.03$). There was no significant effect of parent of origin of the extra X chromosome, skewed X-inactivation, or previous testosterone treatment on performance result.

Academic Achievement

Results from the Wide Range Achievement Test—3rd Edition (WRAT-3) for reading, spelling, and arithmetic subtests are shown in Table I. Mean scores for WRAT-3 reading and spelling fell within the average range, with low average performance observed on the arithmetic subtest. Scores for the group were less than the 25th percentile for reading in 30% (14/47, $P = 0.59$, Chi-squared), for spelling in 38% (18/47, $P = 0.09$, Chi-squared), and for arithmetic in 47% (22/47, $P = 0.008$, Chi-squared). There was no significant effect of age, parent of origin, number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on academic performance.

Attention and Executive Function

On the Conners' Continuous Performance Test (CPT-II), the younger age group produced more omission errors than the normative sample (mean standard score 68.3 ± 34.9) and had increased errors and variability ($P = 0.04$), compared to the older group (Table II). By contrast, mean scores for commission errors were in the normal range in both the younger and older children. There was no significant effect of parent of origin, or number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on performance.

For the Color-Word Interference Test, mean scores for both age groups were within the average range, suggesting age-appropriate performance in this aspect of executive function (ability to inhibit irrelevant or interfering information). There was no significant effect of karyotype, age, or number of

TABLE II. Attention, Verbal Memory, Visual-Motor, and Visual Memory Results (Mean Standard Score ± SD)

	n	Young (<10)	n	Old (≥10.0)	n	Group	*P*-value[a]
Attention							
Conners CPT[b]							
Omissions (more errors = lower SS)	21	68.3 ± 34.9	22	87.8 ± 20.6	43	78.3 ± 29.8	0.03
Commissions (more errors = lower SS)	21	99.0 ± 13.0	22	95.4 ± 16.4	43	97.2 ± 14.8	0.42
Reaction time (increased = lower SS)	21	80.6 ± 20.1	22	92.8 ± 21.4	43	86.8 ± 21.4	0.06
Variability (increased = lower SS)	21	81.7 ± 11.3	22	91.6 ± 17.6	43	86.7 ± 15.5	0.04
Perseverative errors	21	87.9 ± 17.0	22	94.7 ± 13.2	43	91.4 ± 15.4	0.15
DKEFS—Color Word Inference Test[b]							
Inhibition	18	94.9 ± 23.0	25	90.4 ± 15.7	43	92.3 ± 19.0	0.45
Switch	17	97.1 ± 20.9	23	95.3 ± 20.3	40	94.5 ± 18.0	0.45
Verbal memory							
CMS Stories[b]							
Immediate recall	22	92.1 ± 11.6	24	91.7 ± 15.3	46	91.9 ± 13.5	0.93
Delayed recall	21	93.6 ± 14.8	24	91.0 ± 16.5	45	92.2 ± 15.6	0.59
Delayed recognition	19	94.2 ± 18.4	23	98.3 ± 21.1	42	96.4 ± 19.8	0.52
Digit Span[b]							
Digit Span forward	25	93.0 ± 14.4	24	87.7 ± 15.9	49	90.4 ± 15.2	0.23
Digit Span backward	25	90.2 ± 13.1	24	93.5 ± 15.8	49	91.8 ± 14.4	0.42
CVLT[b]							
Trial 1 list A recall	22	93.0 ± 14.6	25	91.9 ± 15.1	47	92.4 ± 14.8	0.81
Trial 5 list A recall	22	85.3 ± 16.0	25	90.1 ± 17.8	47	87.9 ± 17.0	0.34
Learning slope	23	90.5 ± 16.3	25	95.5 ± 16.5	48	93.1 ± 16.4	0.30
Visuo-Motor and Visual Memory							
Rey–Osterrieth Figure[b]							
Copy organization	25	88.5 ± 9.4	21	88.8 ± 18.5	46	88.6 ± 14.1	0.95
Immediate recall organization	24	92.7 ± 8.5	21	90.0 ± 14.8	45	90.9 ± 11.9	0.30
Delay recall organization	23	93.5 ± 8.4	21	90.5 ± 15.9	44	92.1 ± 12.5	0.43
Copy accuracy SS	22	82.3 ± 19.8	24	73.4 ± 29.7	46	77.7 ± 25.6	0.24
Beery Test of VMI[b]							
	21	89.1 ± 13.5	20	84.5 ± 10.8	41	86.8 ± 12.3	0.24

[a]ANOVA by age.
[b]Age-specific norms.

CAG_n repeats on performance. Performance was better in terms of greater cognitive flexibility (capacity to inhibit irrelevant or interfering information processing) in the group with the extra X from the mother versus the father for inhibition (97.9 ± 19.2, $n = 22$ vs. 82.2 ± 15.6, $n = 16$, $P = 0.01$) and switching (101 ± 18.6, $n = 20$ vs. 87.1 ± 14.5, $n = 15$, $P = 0.02$). There was no significant effect of number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on performance.

Verbal Memory

The results from the tests of verbal memory are shown in Table II. On the Children's Memory Scales (CMS), immediate and delayed memory for short story content, as measured by the CMS Stories subtest, fell within the Average range. Memory for Digit Span, as assessed by CMS Numbers, was within the low normal range for recall in both forward and reverse sequence. Performance on the California Verbal Learning Test-II (CVLT-II) was in the average to low average range. There was no significant effect of age, parent of origin, number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on performance.

Visual-Motor Function

On the Beery Developmental Test of Visual-Motor Integration, mean performance was within the low average range (Table II). Copy accuracy and copy organization of the Rey–Osterrieth Complex Figure proved somewhat difficult for the KS subjects, with the overall mean score corresponding to borderline functioning for copy accuracy and the low average range for organization (Table II). There was no significant effect of age, parent of origin, number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on performance.

Language

Word retrieval, assessed with the EOWPVT was normal, as was receptive vocabulary development, as measured by the ROWPVT (Table III). Rapid naming, as measured by the CTOPP subtests, yielded varied levels of performance. Rapid naming of digits and letters fell within the average range and appeared somewhat better than naming of color names and objects, the latter falling in the low average range. Performance on verbal fluency was normal (Table III).

The boys with KS had mean composite standard scores more than 1 SD below the normative sample (<85) on the Test of Language Competence (TLC-E), which assesses linguistic competence in the areas of semantics, syntax, and pragmatics (Table III). Summary scores for expressing intent were lower than for interpreting intent. Mean scores for the younger group were within the average range on the Listening Comprehension and Figurative Language subtests and within the low average range on the Ambiguous Sentences and Oral Expression subtests. Their lowest mean score was the Expressing Intent Composite Score, which evaluates the ability to formulate

TABLE III. Language Results (Mean Standard Score ± SD)

	n	Young (<10)	n	Old (≥10.0)	n	Group	*P*-value[a]
EOWPVT[b]	25	104.5 ± 15.7	25	97.2 ± 11.7	50	100.8 ± 14.2	0.07
ROWPVT[b]	25	102.8 ± 12.3	25	97.8 ± 12.8	50	100.3 ± 12.7	0.17
CTOPP composite[b]							
Rapid naming composite	24	88.8 ± 10.4	25	88.6 ± 19.0	49	88.7 ± 15.3	0.97
Alternative rapid naming composite	20	78.6 ± 16.9	25	81.4 ± 15.9	45	80.1 ± 16.2	0.56
CTOPP Subtest[b]							
Rapid digit naming	20	92.3 ± 7.7	25	91.2 ± 15.9	45	91.7 ± 12.8	0.79
Rapid letter naming	20	91.0 ± 8.5	25	89.8 ± 16.4	45	90.3 ± 13.3	0.77
Rapid color naming	24	84.4 ± 13.0	25	87.8 ± 13.1	49	86.1 ± 13.0	0.36
Rapid object naming	24	80.8 ± 16.6	25	81.0 ± 14.7	49	80.9 ± 15.5	0.97
D-KEFS[b]							
Phonetic fluency	16	95.6 ± 15.8	25	94.4 ± 16.5	41	94.9 ± 16.0	0.82
Semantic fluency	13	100.0 ± 11.6	20	102.0 ± 18.5	33	101.2 ± 15.9	0.73
TLC composite[b]							
Expressing Intent	18	85.2 ± 13.9	25	76.0 ± 10.5	43	79.9 ± 12.8	0.02
Interpreting Intent	17	91.8 ± 12.8	25	79.7 ± 12.5	42	84.6 ± 13.9	0.004
Total Composite Score	16	86.5 ± 13.5	25	75.6 ± 10.0	41	79.9 ± 12.6	0.01
TLC Subtest[b]							
Ambiguous Sentences	21	87.4 ± 12.3	25	78.6 ± 11.3	46	82.6 ± 12.5	0.02
Listening Comprehension	20	94.8 ± 11.4	25	87.4 ± 14.9	45	90.7 ± 13.8	0.08
Oral Expression	18	86.4 ± 15.1	25	79.8 ± 11.9	43	82.6 ± 13.6	0.12
Figurative Language	17	90.9 ± 13.3	25	78.2 ± 11.0	42	83.3 ± 13.4	0.002

[a]ANOVA by age.
[b]Age-specific norms.

propositions in grammatically complete sentences using key words from the context of a given situation (Oral Expression subtest) and the ability to recognize and interpret alternative meanings of vocabulary and structural ambiguities (Ambiguous Sentences subtest).

The older group achieved a mean subtest score within the low average range on the Listening Comprehension subtest with Borderline range scores for the remaining subtests. Performance by the younger group was better than the older group for the Total Composite Score ($P = 0.01$), Expressing Intent Composite Score ($P = 0.02$), Interpreting Intent Composite Score ($P = 0.004$), Ambiguous Sentences ($P = 0.02$), and Figurative Language subtests ($P = 0.002$).

There was no significant effect of handedness, parent of origin, number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on performance of the above tasks.

Motor Skills

The Bruininks–Oseretsky Test of Motor Proficiency (BOT), Lafayette Pegboard, and the PANESS were used to evaluate motor skills (Table IV). On the BOT, the younger and the older groups performed similarly on all but one subtest (Upper Limb Speed and Dexterity) subtest. The mean scores on many of the BOT subtests fell 1 SD or more below the mean of the normative sample (<85), indicating motor skills deficits. Overall, the worst performance was observed on the Running Speed and Agility subtest, which measures running shuttle speed. Also, both groups performed less well than expected for age on the Strength subtest, as measured by ability to perform sit-ups, push-ups, and broad jumps. The performance of the older group on BOT Upper Limb Speed and Dexterity subtest was worse than the younger group ($P = 0.02$) and was the lowest score achieved by the older group. This subtest provides a measure of speeded visual-motor skills such as hand and finger dexterity, hand speed, and arm speed.

The motor function subtests were analyzed according to the group of exclusively right-handed (lateralization index = 100%) combined with exclusively left-handed boys (lateralization index = −100%), versus the remainder of the group. Visual-Motor Control performance on the BOT was better in the 100% right-handed and left-handed group compared to the other-handed group (91.4 ± 17.0, $n = 35$ vs. 77.8 ± 14.0, $n = 15$, $P = 0.01$). This subtest assesses how well hand and visual movements are coordinated on tasks such as cutting paper, completing mazes, and drawing shapes. When the same comparisons were made for the right-handed defined as lateralization index >50%, Visual-Motor Control performance on the BOT was better in the right-handed compared to the non-right-handed group (89.7 ± 18.1, $n = 41$ vs.76.7 ± 12.7, $n = 9$, $P = 0.05$).

There was a trend in the androgen-treated versus non-androgen-treated group for better performance on the BOT subtests Running Speed and Agility (84.7 ± 21.1, $n = 11$ versus 74.0 ± 16.4, $n = 39$, $P = 0.08$) and Visual-Motor Control (95.6 ± 14.1, $n = 9$ vs. 85.0 ± 18.4, $n = 39$, $P = 0.08$). Skewed X-inactivation was associated with increased strength (124 ± 29.7, $n = 2$ vs. 88.5 ± 13.0, $n = 24$, $P = 0.008$). There was no significant effect of parent of origin,

TABLE IV. Motor Function Results (Mean Standard Score ± SD)

	n	Young (<10)	n	Old (≥10.0)	n	Group	*P*-value[a]
BOT composite[b]							
Fine motor composite	25	79.3 ± 17.2	15	76.6 ± 17.2	49	79.1 ± 14.3	0.93
Gross motor composite	24	79.8 ± 20.1	14	74.4 ± 18.1	47	78.5 ± 18.1	0.61
Battery composite	25	77.1 ± 19.1	15	72.9 ± 17.1	48	76.7 ± 17.6	0.87
BOT Subtest[b]							
Running Speed and Agility	25	73.6 ± 14.7	15	74.0 ± 16.7	50	76.4 ± 18.1	0.29
Bilateral coordination	24	88.0 ± 13.8	15	89.0 ± 14.4	49	88.6 ± 13.7	0.79
Strength	23	86.0 ± 11.9	15	78.0 ± 16.7	48	85.4 ± 17.3	0.82
Upper Limb coordination	23	88.1 ± 17.3	15	90.4 ± 17.7	48	90.8 ± 17.0	0.31
Response speed	24	91.3 ± 17.4	15	87.6 ± 25.1	49	89.6 ± 19.0	0.55
Visual-Motor Control	25	82.7 ± 19.5	15	89.8 ± 15.5	50	87.3 ± 17.9	0.07
Upper Limb Speed	25	82.7 ± 11.0	15	69.4 ± 13.8	50	78.2 ± 13.9	0.02
PANESS[b]							
Hand alternating-dominant	18	80.7 ± 31.8	20	84.4 ± 16.6	38	82.6 ± 24.7	0.65
Hand alternating non-dominant	18	86.6 ± 21.6	20	86.5 ± 11.9	38	86.5 ± 16.9	0.99
Hand short dominant	18	96.1 ± 14.4	20	92.4 ± 24.4	38	94.1 ± 20.1	0.58
Hand short non-dominant	18	97.0 ± 12.2	20	92.7 ± 21.1	38	94.7 ± 17.4	0.46
Foot dominant	18	95.8 ± 14.8	20	99.6 ± 19.7	38	97.8 ± 17.4	0.52
Foot non-dominant	18	97.8 ± 14.7	20	93.9 ± 18.9	38	95.7 ± 16.9	0.48
Lafayette Pegboard[b]							
Lafayette Pegboard dominant	22	70.8 ± 42.0	25	76.2 ± 20.1	47	73.7 ± 32.0	0.57
Lafayette Pegboard non-dominant	22	86.4 ± 35.9	25	81.0 ± 19.8	47	83.5 ± 28.3	0.52

[a]ANOVA by age.
[b]Age-specific norms.

number of CAG_n repeats, or skewed X-inactivation on performance.

Selected tests from the Physical and Neurological Examination of Soft Signs (PANESS) were administered. Mean performance was in the average range both for tapping feet and for tapping the index finger to the thumb and was low average when subjects were asked to complete taps of four sequential fingers to thumb. There was no significant effect of age, lateralization, parent of origin, number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on performance.

Mean performance on the Lafayette Pegboard Test (measure of motor dexterity and coordination) was within the borderline range for the dominant hand and low average range for the non-dominant hand. There was no significant effect of age, lateralization, parent of origin, number of CAG_n repeats, skewed X-inactivation, or previous testosterone treatment on performance.

Based on these findings, we include a table summarizing the areas of increased risk and potential remediation for counseling the families (Table V).

DISCUSSION

The goals of this study were to expand the description of the characteristic neuropsychological profile in boys with KS and to examine potential influences on this phenotype, including age, handedness, genetic factors (parental origin of the extra X chromosome, AR CAG_n repeat length, and pattern of X inactivation), and previous testosterone treatment. The results confirm that, as a group, boys with KS may demonstrate atypical neurocognitive development. Our cohort tended to have depressed performance on measures of language development, academic ability, attention, and motor function. In general, the cognitive phenotype is subtle and far from pathognomonic of KS. The descriptive study design did not permit any determination about specificity of the phenotype.

In general, we noted impaired aspects of both verbal and non-verbal cognitive ability. Language abilities were not equally affected. There was relative sparing of vocabulary but impairment of linguistic competence. Also, the boys with KS had an array of motor difficulties, especially in strength, running speed, and agility. Impaired performances on language and motor tests were more prominent in the older age group, while attention problems were more prominent in the younger group.

This raises the question about the effect of androgen deficiency in the older group on performance. We did not observe any significant testosterone-related effects on performance; however the number of testosterone treated boys was small, and administration and age of initiation of testosterone treatment were variable. Thus, the impact of androgen treatment could not be fully addressed in this study and is the subject of future studies.

General Cognition

Consistent with previous studies, our results suggest that general intelligence is within normal limits. However, performance did fall below average for the older group. Previous studies have suggested that lower general intelligence scores in this population were related to selective verbal processing problems, resulting in Depressed Verbal IQ relative to Performance IQ [Ratcliffe et al., 1986; Robinson et al., 1986; Graham et al., 1988; Porter et al., 1988; Walzer et al., 1990; Rovet et al., 1996]. We found that the cognitive issues that serve to lower general intelligence estimates in KS are not specific to language processing problems. In this group, we noted depressed performance on both verbal and non-verbal cognitive ability. While scores were only modestly depressed in the younger age group, older boys with KS had, on average, Verbal Cluster (VC) scores and Nonverbal Reasoning Cluster (NVC) scores more than one standard deviation below the mean of the general population (<85). Strongest performance was seen on one of the Spatial Cluster subtests, Pattern Construction, a measure of visual-constructional ability.

TABLE V. Guide for Counseling Clinicians and Parents

Recognize	Consider
Delayed early expressive language and speech milestones	Early speech therapy and language evaluation
Increased risk for attention deficit without hyperactivity during elementary school	Classroom accommodations, avoid distractions at home when doing homework, medications
Deterioration in school performance in transition from elementary school to middle school	Retesting to discover areas requiring extra attention at or before entrance to middle school
Difficulty with arithmetic at all ages	Request testing and remediation
Increased chance of left-handedness	Writing and sports accommodations
Difficulty with complex language processing: specifically understanding and generating oral language	Language evaluation, Communication through written language, Acquire written notes from lectures
Decreased running speed, agility, and overall strength in childhood	Physical therapy, occupational therapy, Choose sports that emphasize strengths

Language and Achievement

Most males with KS demonstrate difficulties with language and language-based learning from an early age. These anomalies are often observed as delays in early expressive language and speech milestones [Walzer, 1985; Leonard and Sparrow, 1986]. In older boys with KS, significant deficits have been observed in higher order aspects of expressive language such as word retrieval, expressive grammar, and narrative formulation [Robinson et al., 1986; Graham et al., 1988; Walzer et al., 1990], consistent with our results. On a measure assessing higher-level language function (TLC-E), the older subjects in this study demonstrated significant difficulty understanding Figurative Language, interpreting ambiguities in language, and expressing themselves verbally using complete sentences. These findings did not seem to be influenced by genetic factors.

Despite adequate confrontation naming, the results indicate modest difficulties in rapidly retrieving the names of colors and objects. Rapid naming assesses the efficiency of this retrieval of information from long-term or permanent storage, as well as visual scanning. Deficits in rapid naming skills have previously been associated with problems learning to read and/or spell [Denckla and Rudel, 1976]. The KS subjects also demonstrated selective impairment of linguistic skills required to understand and generate oral language and their ability to repeat words presented to each ear was impaired.

Reported problems with receptive language have included deficiencies in phonemic discrimination [Nielsen et al., 1980; Walzer, 1985; Graham et al., 1988; Bender et al., 1993], slower verbal processing speed, and difficulties understanding the grammatical and morphological aspects of language [Walzer et al., 1990]. These difficulties are thought to stem from deficits in auditory temporal processing and working memory [Rovet et al., 1996]. In this KS cohort, receptive vocabulary development, word retrieval, verbal fluency, and verbal memory represented areas of relative strength in language function. The preservation of vocabulary understanding suggests that the cognitive network necessary to acquire, store, and retrieve single words is relatively intact.

The boys with KS across the entire age range in this study produced lower achievement in Arithmetic, with performance below the 25th percentile in 47%. In contrast, performance in reading and spelling achievement fell within the average range.

Attention and Executive Function

Performance of our subjects on a continuous performance test suggested deficits in the ability to sustain attention in the younger subjects (<10 years), without increased impulsivity. Notably, these attention difficulties were not present in the older subjects, suggesting either resolution of the underlying deficit or development of improved strategies to compensate for their attention deficits. There were no obvious deficits in the inhibition, cognitive flexibility, or fluency aspects of executive function.

Visual-Motor and Motor Function

Visual-motor function was relatively impaired, at least in part related to motor function impairment. Motor function was examined using fine motor and gross motor tasks, and measures of strength, speed and agility, and coordination. On portions of the PANESS including repetitive thumb finger tapping and foot tapping, the boys with KS performed at or close to levels expected for age, similar to previous results from Bender et al. [Salbenblatt et al., 1987; Bender et al., 1993]. However as the tasks became more complex (tapping four sequential fingers to thumb), the boys with KS did not perform as well as expected. There are multiple potential explanations for these findings. The more complex tasks require greater utilization of coordination and attention. Androgen deficiency in adolescence may have a negative impact. The worst performance by the younger and older KS groups in the study was on the test of Running Speed and Agility from the BOT, which indexes an array of motor and cognitive skills. Both groups, especially the older, also performed less well than expected for their age on the Strength subtest, as measured by the ability to do sit-ups, push-ups, and broad jumps, and the Upper Limb Speed and Dexterity subtest, which involves timed visual-motor tasks evaluating hand and finger dexterity, hand speed, and arm speed. These motor difficulties are not just of academic interest but have importance for these boys because of psychosocial implications and the likely impaired athletic ability that accompanies these particular deficits.

Lateralization

Non-right-handedness and atypical hemispheric lateralization are important issues in understanding the neurobiology underlying cognitive development and performance in KS. However, data on manual and language asymmetries are contradictory. Netley and Rovet [1982] found an increased incidence of non-right-handedness in KS males, in agreement with our findings. In contrast Geschwind et al. [1998] did not observe increased non-right-handedness in KS. Although subtle differences in how handedness is measured or age of the KS populations studied may account for differences in results, hemispheric lateralization in our KS cohort, as measured by handedness, appears to be atypical.

Atypical lateralization in KS is also supported by previous studies of dichotic listening. Right or left ear advantage in the dichotic listening task reflects the functional dominance of the contralateral hemisphere.

A right ear advantage is observed in most right-handed subjects when the stimuli are verbal, reflecting the left hemisphere dominance for language. Males have a greater right ear advantage than females for verbal stimuli [Netley and Rovet, 1984; Netley et al., 1995; Alexander et al., 1998]. According to our results from this study as well as previous studies, KS males had decreased right ear advantage for dichotic listening for verbal material [Netley and Rovet, 1982]. Also, there was decreased left cerebral perfusion asymmetry in functional neuroimaging [Itti et al., 2003]. Thus in KS males, the left hemisphere may be less dominant for verbal processing/language than would be expected.

Genetic Factors

Despite previous studies suggesting that genetic factors involving the sex chromosomes may influence the phenotype of KS [Iitsuka et al., 2001; Zitzmann et al., 2004], we found very little influence of genetic factors on performance. Previous studies by Zitzmann et al. [2004] reported a significant genotype–phenotype association between smaller number of AR CAG_n repeats with higher academic achievement. In this study, CAG_n repeat length was associated with only a minimal effect on cognition and that effect was in the opposite direction of that reported by Zitzmann. The difference between the results may be related to the Zitzmann population being older and ascertained for different reasons. Zitzmann et al. also used a biallelic weighted mean AR CAG_n repeat length, based on the pattern of X inactivation in peripheral blood leukocytes. We used a simple biallelic mean AR CAG_n repeat length because there is no way to know whether the X-inactivation pattern measured in blood reflects the pattern in the CNS. Weighting did not significantly alter our results (data not shown). Although the human X chromosome has been proposed to carry an imprinted cognitive locus [Skuse et al., 1997], we did not detect a major effect of parent of origin of the extra X chromosome on the KS cognitive phenotype.

The distinctive behavioral and cognitive difficulties in KS reflect anomalies in brain development. Brain development may be altered by androgen deficiency early in life, X chromosome gene excess dosage effects, or both. There is growing evidence from both the neuropsychological profiles and structural and functional neuroimaging studies that the neurocognitive problems observed in KS are not secondary to widespread or diffuse aberrations in neurodevelopment but instead may reflect maldevelopment or dysfunction of specific neural systems.

Implications

The results from this large KS cohort have important neurocognitive and educational implications. From the neurocognitive standpoint, the difficulties present represent an opportunity to gain insights into brain development in boys with KS. Their pattern of relative deficits may be related to atypical lateralization in KS. From the educational standpoint, the average boy with KS in this study did not show a profile that would identify him as "learning disabled" using the standard educational discrepancy formula of impaired achievement relative to general cognitive ability. Therefore, the difficulty in complex language processing and impaired attention as well as motor function identified in the KS population can be missed. This can be a challenge to educators. It is critical that boys with KS are provided with appropriate educational interventions that target their learning challenges in school. These findings would also be an important component of counseling clinicians and families about this disorder.

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