
Neuropsychological Impairment in 42 Adolescents With Sex Chromosome Abnormalities

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Sixty-seven adolescents participated in this protocol, including 42 with sex chromosome abnormalities and 25 controls. Results from a battery of neuropsychological tests indicated karyotype specific patterns of neuropsychological impairment: (1) 47,XXY boys had unimpaired intelligence but reduced abilities in verbal fluency and reading; (2) 47,XXX girls experienced reduced general intelligence accompanied by impaired scores on individual tests of attention, concept formation, spatial thinking, verbal fluency, and academic skills, while retention of memorized information was a relative strength; (3) among the 45,X girls average intelligence level was also reduced along with scores on tests of attention, concept formation, verbal fluency, spatial thinking, and academic skills, and an atypical pattern of hand dominance was identified; (4) test scores in the group of mosaic females did not differ from those of controls. Test scores and patterns of personal adaptation were quite variable in all groups; while eight non-mosaic propositi required intensive special education assistance in their public schooling, eight others have attended college.

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KEY WORDS: neuropsychological impairment, sex chromosome abnormalities

INTRODUCTION

The development of children and adolescents with sex chromosome abnormalities (SCA) has been extensively investigated since it became possible to conduct chromosome screening of a newborn population [Robinson and Puck, 1967]. The prospective studies of SCA individuals

identified in these investigations yielded numerous important discoveries: most of these patients are not profoundly physically malformed, mentally retarded, or behaviorally aberrant, many have mild to moderate developmental and learning problems, and considerable phenotypic variability accompanies all karyotypes [Robinson et al., 1979]. The purpose of these prospective investigations began with the general objective of unraveling the role of sex chromosomes in human development and the consequent disruption of normal development occurring with abnormal amounts of sex chromatin material. As the utilization of prenatal diagnosis has increased exponentially in the past decade, the pursuit of information about the prognosis of SCA infants has similarly intensified. Efforts to define the developmental implications of SCA have focused upon various elements of the phenotype, including physical growth, endocrine function, intelligence, school achievement, motor abilities, and psychological adaptation [Robinson et al., 1979; Stewart, 1982; Ratcliffe and Paul, 1986; Evans et al., 1990]. This neuropsychological investigation was conducted in order to understand the neuropsychological components of childhood learning disabilities and their implications for academic adaptation in SCA adolescents.

METHODS

Subjects

Sixty-seven children participated in this protocol when their chronological age was 14-17 years. Forty-two were children with karyotypic anomalies involving the presence or absence of an X or part of an X chromosome (Table I). These propositi were identified in the course of examining Barr bodies in amniotic membranes obtained from 40,000 consecutive Denver newborns; chromosome abnormalities found in this screening were subsequently confirmed with karyotyping of peripheral blood cells. The nine girls with 45,X or partial X monosomy all have Turner syndrome. The female mosaics have cell lines with 45,X or 47,XXX chromosome constitutions, but in all cases the majority of cells examined were 46,XX, and none of the eight has Turner syndrome. The twenty-five control subjects were all siblings of propositi; from each family was selected no more than one sibling control, closest in age and if possible of the same sex as the propositi.

Received for publication April 5, 1993; revision received May 26, 1993.

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TABLE I. Study Propositi

Karyotype	No. of subjects
47,XXY	14
47,XXX	11
45,X and variants	
45,x	6
46,XXq-	2
45,X/46,X,r(X)	1
Female mosaics	
45,X/46,XX/47,XXX	1
45,X/46,XX	4
46,XX/47,XXX	1
45,X/47,XXX	2
46,XY controls	12
46,XX controls	13

Procedures

All subjects received the following battery of intellectual, academic, and neuropsychological tests. These tests were selected (1) to provide an efficient evaluation of a broad range of cognitive and academic abilities, including intelligence, math and reading skills, language, memory, attention, spatial information processing, and fine motor speed and coordination, and (2) to assess brain functions primarily localized to the right hemisphere (Performance IQ subtests, Math, Spatial Relations Test, left-handed Finger Tapping and Grooved Pegboard), left hemisphere (Verbal IQ subtests, Reading, Boston Naming Test, Auditory Verbal Learning Test, right-handed Finger Tapping and Grooved Pegboard), and frontal lobes (Trail Making Test, Wisconsin Card Sorting Test).

Test	Skills measured
Wechsler Intelligence Scale for Children-Revised	Intelligence
Woodcock-Johnson Psychoeducational Battery	
Math Cluster	Mathematics
Reading Cluster	Reading
Spatial Relations Test	Two-dimensional rotation
Trail Making Test	Attention, search, mental flexibility
Boston Naming Test	Expressive language/word retrieval
Auditory Verbal Learning Test	Verbal learning/memory
Wisconsin Card Sorting Test	Concept formation, ability to shift and maintain mental set, perseverative thinking
Finger Tapping	Motor speed, bilateral
Grooved Pegboard	Motor speed and coordination, bilateral

RESULTS

Table II includes test score means and standard errors for controls and each of the four propositi groups. With the exception of **Tapping** and Grooved Pegboard, all results are expressed as age-standardized quotient scores with mean of 100 and standard deviation of 15. Due to

small sample size, the assumptions of equal group **variance** and normal distribution necessary for parametric data analyses were not met. Consequently, a one-way analysis of variance was performed on the ranked data. Significant between-group differences ($P < .05$) were recorded for all test scores except the Verbal **IQ-Performance** IQ difference score, and the dominant and **non-dominant** hand scores from the Tapping and Grooved Pegboard Tests. Dunnett's multiple comparisons procedure was used on the ranked data to determine which group medians differed from the control group ($P < .05$). P values represent these differences between medians, which are not included in Table II but in all cases were similar to mean scores. Results are described by **karyotype group**.

47,XXY

Intelligence (full scale IQ) and concept formation skills (Wisconsin Card Sorting Test) did not differ significantly from controls, although IQ scores do suggest somewhat reduced general intellectual ability (Table II). Auditory Verbal Learning Test and Boston Naming Test scores indicate diminished verbal fluency and memory. This reduction in language skills is consistent with academic test results demonstrating reduced reading scores but unaffected math skills. Finally, the mean **47,XXY Trail Making** Test score was 19 points lower than that of controls, indicating difficulty in this group with rapid sequencing of numbers and letters.

47,xXx

The significantly reduced mean full scale IQ (84.4) in this group appears to be the lowest of any of the propositi groups. Most of the remaining tests are similarly reduced, indicating deficits in attention, concept formation, **mental flexibility, spatial thinking, verbal fluency,** and basic academic skills (Table II). The one exception to this pattern of comprehensive skill impairment is the finding of relatively strong verbal learning skills, as seen in results from the Auditory Verbal Learning Test.

45,x

The full scale IQ in this group was significantly lower than that of controls. Not surprisingly, this finding was accompanied by low scores on Math, Reading, Spatial Relations Test, Trail Making Test, Boston Naming Test, Auditory Verbal Learning Test, and Wisconsin Card Sorting Test (Table II). While mean dominant and **non-dominant** hand scores on Finger Tapping and Grooved Pegboard did not differ from those of controls, the 45,X group alone demonstrated dominant-nondominant hand splits on the two tests which differed significantly from those of controls. Thus, the dominant hand superiority in performing the Finger Tapping and Grooved Pegboard Tests was significantly less in the 45,X group than in the control group.

Mosaic

Mean scores for the eight mosaic females did not differ significantly from controls on any of the 16 measures (Table II). As seen in their full scale IQ of 106.5, these adolescents demonstrate age-appropriate intellectual

TABLE II. Neuropsychological Test Scores (Mean and Standard Error) for Each of the Five Karyotype Groups

	47,XXY N = 14	47,XXX N = 11	45,x N = 9	Mosaic N = 8	Control N = 25
Verbal IQ	97.9 (4.34)	97.4 (6.14)	99.0 (6.95)	97.5 (5.56)	97.6 (2.34)
performance IQ	99.5 (2.90)	100.2 (4.61)	97.8 (6.62)	99.1 (5.49)	99.9 (2.39)
Verbal IQ-Performance IQ difference score	-1.60 (3.34)	-2.80 (3.09)	1.20 (4.91)	-1.60 (3.27)	-2.30 (2.21)
Full Scale IQ	96.3 (3.64)	84.4* (5.63)	88.2* (7.02)	106.5 (5.27)	106.4 (2.31)
Math (cluster score)	99.7 (2.57)	84.1* (4.50)	81.8* (4.17)	109.5 (5.84)	102.8 (2.98)
Reading (cluster score)	83.9* (3.36)	88.0* (3.79)	83.2* (5.77)	109.0 (5.08)	105.5 (2.75)
Spatial Relations Test	97.0 (4.50)	89.9* (5.30)	82.2* (6.68)	109.3 (2.92)	109.7 (3.37)
Trail Making Test (part B)	80.4* (4.33)	74.6* (5.32)	65.0* (6.37)	95.3 (3.93)	99.4 (4.45)
Boston Naming Test (total naming score)	72.9* (3.81)	70.2* (8.56)	76.8 (8.71)	86.8 (6.04)	81.5 (4.42)
Auditory Verbal Learning Test (average recall score)	79.3* (3.62)	91.2 (5.35)	70.6* (7.77)	111.2 (3.09)	100.1 (3.52)
Wisconsin Card Sorting Test (perseverative error score)	98.1 (3.66)	82.2* (5.03)	77.3* (6.52)	102.0 (5.60)	96.7 (2.75)
Tapping (no. of taps in 10 sec)					
Dominant hand	45.5 (1.09)	42.0 (2.87)	39.5 (2.20)	47.8 (1.92)	46.7 (1.78)
Nondominant hand	41.2 (1.38)	40.2 (1.56)	37.7 (1.31)	42.0 (0.75)	39.9 (1.43)
Dominant-nondominant hand	4.33 (0.80)	1.83 (2.24)	1.73* (1.53)	5.73 (1.59)	6.87 (1.20)
Grooved Pegboard (time to completion)					
Dominant hand	69.9 (2.35)	68.6 (6.58)	79.4 (4.40)	59.00 (5.81)	64.1 (3.80)
Nondominant hand	77.5 (3.70)	73.6 (6.68)	77.1 (5.47)	62.8 (2.70)	72.4 (3.15)
Dominant-nondominant hand	-7.69 (2.81)	-5.00 (1.92)	2.30* (3.52)	-3.80 (6.13)	-8.29 (2.3)

* Significantly different from controls (Dunnett's multiple comparisons test).

ability, and no areas of relative deficiency were found on the measures of academic skills, spatial thinking, language, memory, concept formation, or motor skills.

DISCUSSION

Although mental retardation is rare in this population, SCA adolescents demonstrate significant neuropsychological impairment. This finding is not surprising given that learning disabilities are frequently diagnosed in SCA children [Bender et al., 1991; Pennington et al., 1982]; in our group of 34 nonmosaic propositi, fully 79% (27) received special education intervention from their schools before reaching adolescence [Bender et al., 1991]. Two additional findings are immediately impressive. First, there is considerable phenotypic variability among the 34 nonmosaic propositi. While eight children required intensive special education intervention in self-contained classrooms for severely learning disabled children, seven required no formal assistance to complete their public schooling, and eight have attended college [Bender et al., 1986]. The standard error accompanying all test score means (Table II) similarly indicates that while SCA introduces a genetically imposed risk for neuropsychological im-

pairment, the ultimate neuropsychological phenotype is dependent upon a large number of interactive genetic and environmental variables [Decker and Bender, 1988]. The impact of environment has been shown to be particularly significant for SCA children; the development of these children is much more similar to siblings in the presence of a stable and nurturant family environment, while family dysfunction is associated with significantly more emotional and developmental debilitation in the propositi than in their brothers and sisters [Bender et al., 1987].

The second notable finding to emerge from these data is the karyotype specificity of neuropsychological impairment. Although sample size in the individual karyotype groups is small, results are similar to childhood reports in other unselected groups [Robinson et al., 1990]. While each of the three nonmosaic propositi groups has aneuploidy of a single chromosome, neurocognitive development is differentially affected by the nature of the anomaly. This is particularly striking in the case of 47,XXY boys and 47,XXX girls because, while both groups have one additional X chromosome, their learning and neuropsychological difficulties are quite different.

Language impairment associated with the 47,XXY karyotype is well-documented [Bender et al., 1983; Graham et al., 1988]. The marked difficulties seen in these results from the Auditory Verbal Learning Test and Boston Naming Test are consistent with findings that 47,XXY boys frequently demonstrate impairment in verbal memory, retrieval, fluency, and processing speed [Bender et al., 1983; Graham et al., 1988; Bender et al., 1989]. Several investigators have presented evidence that the language deficits of 47,XXY boys are captured in Wechsler Intelligence Scale for Children results that include a verbal IQ significantly lower than performance IQ [Graham, et al., 1988; Netley, 1983]. Others have reported no significant verbal IQ-performance IQ split [Ratcliffe et al., 1982] even when, as indicated here, results from concurrently administered tests reveal specific language processing deficits. Impairments of verbal memory, fluency, and speed of verbal information processing [Bender et al., 1983; Graham et al., 1988; Bender et al., 1989] are likely not measured well by the Wechsler scales, although a reduction in verbal IQ may occur when other language processes are affected. While math skills remain relatively intact, reading ability in 47,XXY adolescents continues to be selectively affected. Reading disability occurred in 32 of 43 47,XXY boys (74%) in three studies of unselected propositi [Bender et al., 1991; Ratcliffe et al., 1986; Graham et al., 1988], and has been linked to related deficits in phonic analysis [Graham et al., 1988] and verbal fluency [Bender et al., 1986]. The significantly lowered Trail Making Test score likely reflects the reduced speed of processing reported among 47,XXY boys [Bender et al., 1983, 1989] and not difficulty with attention or strategic information processing, particularly given the strong Wisconsin Card Sorting Test performance. Even among the brightest 47,XXY adolescents, three of whom have attended college, these difficulties with verbal fluency, reading, and speed of information processing have required the selection of a moderately competitive college offering the opportunity for supplementary academic support. These 47,XXY language-based processing deficits remain the most homogeneous and consistent cognitive impairment found in any SCA group, and have been repeatedly cited as evidence of a genetically mediated left-hemisphere dysfunction [Graham et al., 1988; Bender et al., 1986, 1989].

The general intellectual impairment found among 47,XXX girls is seen in their full scale IQ, which is 22 points lower than that of controls. Less clearly understood is the possibility of karyotype-specific strengths and weaknesses, in addition to this generally reduced intellectual capacity. Although no significant verbal-performance IQ differences were documented in the 47,XXX adolescent group, Wechsler Intelligence Scale for Children test results from 32 47,XXX girls from Scotland, Canada, and the United States included mean verbal and performance IQs of 86.6 and 95.2, respectively [Evans et al., 1990]. The possibility of a specific language impairment in 47,XXX girls was further supported by evidence of marked difficulty performing a sentence verification task [Netley, 1983], and by evidence of an impairment in auditory short-term memory

[Rovet and Netley, 1983]. Clearly, the language impairment in 47,XXX girls is not as specific as that found in 47,XXY boys, and most probably reflects bilateral as well as left-hemisphere based brain dysfunction [Bender et al., 1986, 1989]. Memory capacities in this group present a particularly intriguing puzzle. 47,XXX girls were previously reported to be relatively adept on a test of word fluency [Bender et al., 1989]; similar strength demonstrated here on a learning test involving repeated exposure to the same word list suggests that although 47,XXX adolescents have depressed language skills and may have some difficulty with the initial acquisition of verbal information, their ability to retain and retrieve previously learned information is a strength. Nine of the 11 47,XXX girls in this study received special education intervention for a variety of academic deficits, and one was placed in a full-time class for mentally retarded children [Bender et al., 1991]. Two of the 47,XXX girls have attended and one has completed college; it appears at this time unlikely that any of the remaining nine will enter college.

The prevalence of leaning disabilities and diminished cognitive abilities reported previously in the group of 45,X girls [Pennington et al., 1982; Bender et al., 1984, 1991] persists in adolescence and is seen here with reduced scores on a variety of neuropsychological and academic tests and a full scale IQ which is 18 points lower than that of controls. Girls and women with Turner syndrome are widely reported to have a specific deficit in spatial thinking skills but relatively normal verbal abilities and general intelligence, suggesting impeded right-hemisphere functioning [Garron, 1977; Rovet, 1990]. Results from this evaluation of nine 45,X adolescents indicates generally impaired skills, including verbal IQ, performance IQ, reading ability, and problem solving skills, rather than specific spatial impairment. Despite this, three girls experienced no learning difficulties in childhood and have attended college. This small sample may be biased with an over-representation of cognitively impaired Turner syndrome subjects. In other study cohorts the level of cognitive functioning and academic adaptation appears to be higher. In a review of 13 studies with 226 Turner syndrome subjects, Rovet [1990] reported an average reduction in verbal IQ of 4 points and an average reduction in performance IQ of 15 points relative to a combined group of 142 controls, suggesting that many Turner syndrome girls may experience subtle deficits in verbal/conceptual skills accompanied by more dramatic deficits in perceptual/spatial skills. The nature of this spatial impairment is heterogeneous [Bender et al., 1983]; the marked psychological variability seen across Turner syndrome subjects has not been successfully traced to variations in their karyotype [Bender et al., 1984; Rovet, 1990].

The 45,X group alone demonstrated an atypical pattern of handedness. While all were right-handed, their dominant hand superiority on Finger Tapping and the Grooved Pegboard Test was less than that of controls. Although both the 45,X and 47,XXX groups have similar histories of significant impairment in neuromotor development [Salbenblatt et al., 1989], the presence of poorly established dominant hand superiority only in

the 45,X group suggests atypical development of hemispheric organization and specialization. Rovet and Netley (1982) have argued that disruption in the hemispheric specialization of TS individuals has occurred because verbal functioning, primarily located in the left hemisphere of normal women, is more diffusely distributed between the right and left hemispheres in TS women, with the result that these individuals may demonstrate impairment of left as well as right hemisphere functions. While the present data support this conclusion, further evidence from larger, and perhaps less biased, samples of TS subjects will be necessary to establish the validity of this model.

The eight mosaic females, none of whose scores differs from controls, appear to be relatively unaffected by their karyotype. None required special education intervention, and three have attended college. Indeed, in all cases the majority of cells studied in these individuals are euploid. While this small group includes four different mosaic karyotypes involving 45,X or 47,XXX anomalies, evidence from the combined international cohort of 16 unselected mosaic subjects similarly indicates that neither 45,X mosaics nor 47,XXX mosaics often demonstrate developmental deficits relative to chromosomally normal controls. The presence of these developmentally normal adolescents thus provides further evidence that neuropsychological impairment in nonmosaic SCA adolescents is a result of the neurodevelopmental impact of their SCA and not the result of participation in a longitudinal study (Puck, 1981).

SUMMARY

In this longitudinal study of 42 adolescents with sex chromosome abnormalities (SCA), patterns of neuropsychological impairment indicate karyotype-specific influence of the SCA. 47,XXY boys had reduced scores on tests of language fluency and reading when compared to 25 sibling controls. 47,XXX girls were impaired on almost all neuropsychological tests but demonstrated relative strength in their ability to retain previously learned information. 45,X girls also demonstrated global impairment of intellectual functioning along with a pattern of atypical motor dominance. Test scores of the SCA mosaic girls who remain relatively unaffected by their SCA were not different from those of controls. The abilities of propositi in all four groups were quite variable. Some children required special education throughout their public schooling, while others advanced proficiently; eight have attended college. Generalizations here are limited by small sample size. The ultimate adult academic and vocational adaptation of the SCA adolescent group is the subject of this continuing investigation.

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