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BRIEF REPORT

The Structural Brain Correlates of Cognitive Deficits in Adults with Klinefelter's Syndrome

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Context: Adults with Klinefelter's syndrome (KS) are known to present disturbances of language skills and delayed learning abilities.

Objectives: The aim of this study was to assess brain morphometry in KS and to correlate eventual volumetric changes with performance on neuropsychological tests.

Patients: Patients included 18 KS adults and 20 age-matched controls.

Methods: All participants underwent prospectively double-spin-echo brain magnetic resonance imaging and neuropsychological testing of verbal and nonverbal domains. On the axial stack of magnetic resonance imaging slices, regional brain volumes were measured either by automated segmentation (full brain, total cerebrospinal fluid, and ventricular volume) or manual drawing with help of a neuroanatomy atlas (frontal, temporal, and parietal lobes, gray matter component of the lobes, cerebellar hemispheres, and hippocampal complexes).

Results: KS patients performed significantly lower than controls on language-related tasks exploring verbal processing speed and verbal executive function. They were diagnosed with significant enlargement of ventricular volume and bilateral reduction of cerebellar hemispheres. Furthermore, after separation of participants according to handedness and after correction of regional brain volumes for atrophy, a significant reduction of left temporal lobe volume was found in KS compared with controls. Ventricular volume was inversely correlated with cognitive function, whereas left temporal lobe volume was positively correlated with language-related tasks.

Conclusion: This study hypothesizes that supernumerary X-chromosome and/or congenital hypogonadism provoke structural alterations in the subcortical pathways involved in language processing, thus providing a neurobiological substrate for cognitive deficits in KS.
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KLINEFELTER'S SYNDROME (KS) is the most common sex-chromosome aneuploidy in humans with a prevalence of 0.1–0.2% phenotypic boys (1). Presence of one (47,XXY) or more extra X-chromosomes is responsible for lower testosterone production and impaired spermatogenesis, clinically identified at puberty by overt features including small testes, infertility, and gynecomastia (1, 2). KS adolescents also are described as having a general typical appearance, with taller stature and smaller head perimeter (1, 3).

Besides endocrinological manifestations, numerous studies have depicted a characteristic pattern of cognitive and behavioral deficits in KS, mostly learning disabilities in reading/spelling and deficits in language processing (3–7). Specific impairment of language development has led to speculation on a left-hemisphere dysfunction, possibly via alteration in the typical pattern of cerebral dominance, *i.e.* a loss of temporal leftward asymmetry (5, 8). Magnetic resonance imaging (MRI) has demonstrated left temporal gray matter volume reduction in 10 KS adults (9). Another MRI study failed to demonstrate lobar asymmetries but rather highlighted reduction of total-brain volume and enlargement of lateral ventricles in 10 KS adults (10).

Goals of the present study were to assess brain morphometry in 18 KS adults controlled for handedness compared with 20 controls and to correlate eventual volumetric changes with neuropsychological performance.

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Abbreviations: CSF, Cerebrospinal fluid; KS, Klinefelter's syndrome; MRI, magnetic resonance imaging; VOI, volume of interest.

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Subjects and Methods

Subjects

We studied prospectively 18 KS men (18–63 yr), recruited from a population followed periodically in our institution for management of hypogonadism. None were specifically selected for behavioral or cognitive abnormalities, and 15 were right-handed. At the time of study, 10 patients were under testosterone treatment with a heterogeneous duration ranging from 3 to 60 months. For comparison purposes, we enrolled 20 age-matched control men (18–57 yr), exempt of neuropsychiatric conditions based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, of whom 15 were right-handed. The study was approved by our Institutional Review Board; all participants gave informed written consents, were fluent in English, and underwent both neuropsychological testing and brain MRI within 1 month.

Neuropsychological assessment

Subjects were administered a comprehensive 4-h neuropsychological battery specially designed to explore verbal and nonverbal cognitive

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domains (Table 1). Complete lists of tests and specific variables used for analysis have been detailed previously (11). Because the assessment of some domains required combining the performance on at least two independent tests, the different raw test scores (n = 38) were converted into standard equivalents (Z-scores) using a normal database and then averaged for each functional domain (n = 14) to simplify statistical analysis (11).

MRI procedure

Imaging was performed on a 1.5-Tesla Signa scanner (General Electric, Milwaukee, WI). A total of 26–30 contiguous axial slices were acquired in the Talairach plane, covering the entire encephalon from cerebellum to vertex. A double-spin-echo MRI sequence was chosen for best gray/white/cerebrospinal contrasts: repetition time, 2000 ms; echo times, 20 and 100 ms; number of excitations, 1; matrix, 256 × 256; field of view, 240 mm; slice thickness, 5 mm with no gap.

Image processing

MRI stacks of axial slices (second echo, T2-weighted) were processed using a custom software suite of morphometry tools (12) to extract various volumes of interest (VOIs). External encephalic contour was extracted (whole-brain, cerebellum) using a histogram thresholding and erosion/dilatation. Total ventricular volume (lateral ventricles, third and fourth ventricles) and total cerebrospinal fluid (CSF) volume were extracted using a "bucket paint" algorithm (automatic three-dimensional flooding) empirically optimized for T2-weighted images.

Furthermore, specific VOIs were manually drawn on all related slices around the frontal, temporal, and parietal lobes, as well as around the cerebellar hemispheres, from the interhemispheric midline to the external surface. VOIs were also drawn around the gray matter component within each lobe, following rigorously the white/gray interface and the same external surface, and around the hippocampal complexes. These VOIs were drawn by one radiologist (5 h/patient) with the help of a neuroanatomy atlas and carefully quality controlled by another radiologist on all slices (1 h/patient). Observers were blinded to patient status and cognitive profiles. Finally, raw MRI volumes were subtracted from CSF to obtain VOIs of atrophy-corrected neuronal tissue (12).

Statistical analysis

Comparisons of demographical data, neuropsychological scores, and MRI volumes between KS and controls were conducted with Statview 5.0 (SAS Institute, Cary, NC), using unpaired Student *t* test (entire populations) and ANOVA with Fisher's *post hoc* test (subpopulations according to handedness and testosterone supplementation). Linear regression was performed between MRI volumes and neuropsychological scores. To control for multiple comparisons, *P* values were lowered to 0.01.

Results

Neurocognitive profiles

Population scores on neuropsychological tests are summarized in Table 1. KS patients performed significantly lower than controls on language-related tasks exploring processing speed and executive function, consistent with previous findings (11). A trend for lower performance was also found on nonverbal processing speed, verbal attention, motor speed, language, and nonverbal executive function.

MRI results

Differences in MRI volumes between KS and controls are displayed in Table 2. KS patients were diagnosed with significant enlargement of ventricular volume and bilateral reduction of cerebellar hemispheres, slightly more marked on the right side. A trend for reduced total-brain volume was seen in KS. In addition, frontal, parietal, and temporal gray matter volumes were slightly more reduced on the left side, although not significantly. In contrast, subcortical structures such as the hippocampal complexes and the cerebellar hemispheres appeared slightly more reduced on the right side.

Influence of handedness

When using CSF-corrected VOIs, reduction of cerebellar hemispheres was confirmed in the right-handed KS patients compared with the right-handed controls. Of interest, a significant reduction of left temporal lobe volume was now highlighted in the right-handed KS, which was not suggested previously when handedness was uncontrolled. No significant differences in MRI volumes were found between left-handed KS patients and controls.

TABLE 1. Demographics, IQ (raw scores), and neuropsychological performances (Z-scores) in the population studied

Variables	KS patients (n = 18)	Normal controls (n = 20)	Unpaired *t* test (*P* value)
Age (yr)	35.8 ± 11.8	32.3 ± 11.3	NS
Education (yr)	12.9 ± 2.2	13.2 ± 1.7	NS
Intelligence			
Verbal IQ	98.9 ± 16.2	98.9 ± 11.8	NS
Performance IQ	101.1 ± 10.1	101.6 ± 16.2	NS
Full-scale IQ	99.5 ± 11.8	99.5 ± 11.3	NS
Verbal attention	−0.72 ± 1.45	0.07 ± 1.08	0.09
Language	−0.69 ± 1.33	−0.07 ± 0.71	0.1
Spatial/constructional ability	−0.56 ± 1.30	−0.16 ± 1.11	NS
Information processing speed			
Verbal	−1.37 ± 1.53	0.16 ± 0.91	0.006[a]
Nonverbal	−0.61 ± 0.77	−0.04 ± 0.77	0.05
Memory			
Verbal	−0.12 ± 0.77	−0.06 ± 0.80	NS
Nonverbal	−0.15 ± 1.02	0.07 ± 0.66	NS
Executive			
Verbal	−0.90 ± 0.96	−0.05 ± 0.58	0.005[a]
Nonverbal	−0.54 ± 0.93	−0.09 ± 0.63	0.1
Arithmetic	−0.26 ± 0.65	−0.12 ± 0.85	NS
Motor speed	−0.72 ± 1.28	−0.09 ± 1.00	0.1

IQ, Intelligence quotient; NS, not significant.
[a] Significance after correction for multiple comparisons (*P* value lowered to 0.01).

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TABLE 2. Differences in brain MRI volumes between KS patients and controls, in the entire population (raw volumes) and after separation according to handedness (atrophy-corrected volumes)

Raw brain volumes	KS patients (n = 18)	Controls (n = 20)	Unpaired *t* test (*P* value)
Total brain	1411.7 ± 95.1	1502.1 ± 158.8	0.04
Total ventricular volume	34.3 ± 11.0	23.5 ± 10.1	0.003[a]
Total CSF	143.0 ± 30.3	147.1 ± 23.0	NS
Right frontal lobe (gray matter)	231.7 ± 21.9 (163.3 ± 15.8)	250.6 ± 23.1 (172.8 ± 16.2)	0.02 (0.08)
Left frontal lobe (gray matter)	230.2 ± 24.6 (160.9 ± 15.8)	246.0 ± 21.4 (172.0 ± 15.2)	0.04 (0.03)
Right temporal lobe (gray matter)	220.5 ± 14.2 (99.4 ± 7.5)	234.3 ± 24.4 (106.1 ± 11.5)	0.04 (0.04)
Left temporal lobe (gray matter)	217.1 ± 13.7 (97.7 ± 8.3)	230.5 ± 20.1 (104.6 ± 9.4)	0.02 (0.02)
Right parietal lobe (gray matter)	111.5 ± 19.7 (78.1 ± 13.9)	122.3 ± 29.2 (86.3 ± 17.5)	NS (NS)
Left parietal lobe (gray matter)	107.0 ± 17.1 (75.2 ± 11.3)	124.6 ± 28.0 (85.4 ± 16.1)	0.03 (0.03)
Right hippocampal complex	9.9 ± 0.9	10.4 ± 0.8	0.1
Left hippocampal complex	10.4 ± 1.0	10.3 ± 0.9	NS
Right cerebellar hemisphere	51.8 ± 4.4	58.7 ± 6.8	0.0007[a]
Left cerebellar hemisphere	52.2 ± 3.6	58.6 ± 7.0	0.001[a]
Atrophy-corrected brain volumes	**Right-handed KS (n = 15)**	**Right-handed controls (n = 15)**	**ANOVA**
Total brain	1403. ± 101.4	1499.9 ± 166.3	0.06
Right frontal lobe (gray matter)	202.0 ± 20.6 (139.1 ± 14.9)	215.3 ± 22.7 (141.4 ± 15.5)	0.1 (NS)
Left frontal lobe (gray matter)	203.4 ± 24.1 (138.9 ± 15.5)	216.1 ± 21.2 (144.1 ± 15.4)	NS (NS)
Right temporal lobe (gray matter)	192.8 ± 13.0 (89.5 ± 7.2)	210.1 ± 25.0 (95.6 ± 11.4)	0.02 (0.09)
Left temporal lobe (gray matter)	192.7 ± 13.3 (88.6 ± 8.4)	210.4 ± 19.5 (96.5 ± 9.1)	0.006[a] (0.02)
Right parietal lobe (gray matter)	98.4 ± 18.8 (67.6 ± 12.3)	109.6 ± 25.2 (74.5 ± 15.2)	NS (NS)
Left parietal lobe (gray matter)	94.9 ± 15.7 (65.4 ± 9.3)	113.9 ± 24.8 (74.9 ± 14.7)	0.02 (0.04)
Right hippocampal complex	8.9 ± 1.2	9.1 ± 1.2	NS
Left hippocampal complex	9.4 ± 1.4	9.4 ± 1.1	NS
Right cerebellar hemisphere	49.5 ± 4.5	56.3 ± 6.5	0.002[a]
Left cerebellar hemisphere	49.7 ± 4.1	56.2 ± 6.7	0.003[a]

Data are expressed in milliliters (mean ± SD). NS, Not significant.
[a] Significance after correction for multiple comparisons (*P* value lowered to 0.01).

Influence of testosterone supplementation

No significant difference in neuropsychological performance was found between testosterone-treated and testosterone-naive patients. Only a trend for lower motor skills was found in testosterone-treated patients. Similarly, no significant influence of testosterone therapy on MRI volumes was found, except for a trend for smaller right hippocampal complex and left cerebellar hemisphere in testosterone-treated right-handed patients.

Correlations between MRI and cognitive findings

Abnormal MRI volumes were plotted against scores on neuropsychological tests in each of the 14 explored domains (Table 3). Of interest, ventricular volume was inversely correlated with verbal processing speed and verbal executive function, two neuropsychological domains significantly impaired in KS. Ventricular volume was also inversely correlated with nonverbal processing speed (which was depressed to a lesser extent in KS). In contrast, left temporal lobe volume (and not its gray matter component) was positively correlated with language scores and verbal processing speed in the subset of right-handed participants, indicating that the larger the left temporal lobe, the higher the performance on language-related tasks. No significant relationship was found between cerebellar volumes and neuropsychological skills.

Discussion

KS patients represent a combined study model for genetics, hypogonadism, and dyslexia. In childhood, language difficulties start with a learning delay in reading/spelling, which remarkably resembles that of cytogenetically normal

TABLE 3. Regression analysis between abnormal MRI volumes (found to be abnormal in Table 2) and scores on neuropsychological tests

Regional brain volumes	Cognitive domains	r coefficient	*P* value
Total ventricular volume[a]	Verbal processing speed	−0.63	0.0001
	Nonverbal processing speed	−0.51	0.003
	Verbal executive	−0.51	0.003
Left temporal lobe[b]	Language	+0.51	0.01
	Verbal processing speed	+0.50	0.01
Right cerebellar hemisphere[b]	None		
Left cerebellar hemisphere[b]	None		

Positive r values indicate positive relationship, and negative r values indicate inverse relationship. To correct for multiple comparisons, only regression analysis results showing r ≥ 0.5 are displayed.
[a] Statistical analysis performed on the entire population (18 KS plus 20 controls).
[b] Statistical analysis performed on the right-handed only (15 KS plus 15 controls).

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dyslexic children (6, 8). Language impairment is usually contrasted with preservation of visuospatial abilities and general intelligence (3–7). In adulthood, the few data available suggest that verbal deficits persist in a subset of patients (8, 11), but additional profiles may emerge later, including preferential impairment of visuospatial and motor abilities (11). In our study, verbal processing speed and executive function were significantly suppressed, which may affect everyday life for concept formation, problem solving, task switching, inhibitory processes, speed of response, and planning. Delayed learning skills to seek food was also demonstrated recently in XXY mice, providing additional evidence that the behavioral phenotype is inherent to the sex-chromosome aneuploidy and not the result of social impairment (13).

According to the Wernicke-Geschwind model, language is actuated by a wide cerebral network preferentially distributed in the perisylvian cortex of the left hemisphere in most right-handers, supported by a striking anatomical asymmetry of the planum temporale (14). Loss of this typical pattern is seen in many left-handers, a state referred to as "anomalous cerebral dominance" (14). Functional neuroimaging studies have also suggested that language lateralization may be genetically influenced, *e.g.* showing increased bilaterality in women (15) and blood flow elevation in right-hemisphere areas, possibly considered as the mirrored language areas in KS (16). Morphologically, anomalous cerebral dominance was not evident in the present study, except for the left temporal lobe volume reduction found in right-handed KS patients. This reduction was significant for the whole lobe but not for the gray matter alone, in contrast with a previous study (9). Possible explanations for such discrepancy might reside in the difference of population age ranges between studies (18–63 *vs.* 24–32 yr, respectively), due to the prevalence of cortical atrophy, or in the difference of MRI spatial resolution (5 *vs.* 1.5 mm slice thickness, respectively). However, the most plausible explanation is that KS patients were not explicitly controlled for handedness in the previous report (9).

Rather than cortical alterations, we demonstrate significant structural changes in subcortical areas. It is hypothesized that ventricle enlargement may have an impact on the neighboring white matter. Indeed, the Wernicke-Geschwind model formulates the interactions between the posterior temporoparietal language system and the anterior ventroposterior frontal language system through subcortical pathways, including the arcuate fasciculus and brainstem. Therefore, ventricle enlargement found in KS, in our study as well as in another (10), may interrupt these pathways, all the more because total-brain volume tends to be reduced. The hypothesis of a disconnection between anterior and posterior language systems has been raised in dyslexics using functional imaging and verbal tasks (17, 18). This hypothesis is anatomically supported in our study by the inverse relationships found between ventricular volumes and verbal performances. Nonverbal functions were found impaired to a lesser extent, although an inverse relationship was seen between ventricle enlargement and nonverbal processing speed. Bilateral reduction of cerebellar hemispheres may also account for verbal and nonverbal disabilities, because the cerebellum is involved in a wide range of tasks, including motor synchronization. This could participate in the coordination deficiencies reported in KS (7), but, in our study, no formal cerebellar testing was performed.

Whether the neurocognitive phenotype of KS adults is a direct consequence of low testosterone stimulation remains controversial because postnatal androgen deficiency does not often appear until puberty (7, 8). Moreover, patients presenting with other supernumerary sex-chromosome aneuploidies (47,XXX, 47,XYY) have opposing gonadal dysfunction but remarkably overlap in terms of cognitive profiles (3, 7). Therefore, a genetic contribution from the pseudoautosomal locus (homologous X-Y region) seems the most plausible explanation (8). The hypothesis of an alteration in gene dosage in this locus is further supported by the fact that Turner 45,X0 patients demonstrate a mirrored pattern of cognitive deficits, with remarkable preservation of verbal skills contrasted with severe impairment of visuospatial skills (4). Our series failed to demonstrate an influence of testosterone on cognition or brain volumes, but we are cautious in interpreting this observation because treatment was uncontrolled and began during or after adolescence. Some data suggest lower neonatal testosterone levels in XXY *vs.* XY infants (19) that could influence neurocognitive domains but not be influenced by later treatment. Hormone responsiveness, particularly androgen receptor gene polymorphisms (CAGn length), may also account for behavioral/cognitive outcome of KS and impact on patient treatment (20, 21).

To conclude, this study hypothesizes that supernumerary X-chromosome and/or congenital hypogonadism provoke structural alterations in the subcortical pathways involved in language processing, thus providing a neurobiological substrate for cognitive deficits in KS. Additional studies using task-specific brain activation procedures might be useful to sustain our conclusions.

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