Original article

https://doi.org/10.6065/apem.2244222.111
Ann Pediatr Endocrinol Metab 2023;28:258-266

Annals of Pediatric Endocrinology & Metabolism
apem

Neurocognitive and psychosocial profiles of children with Turner syndrome

So Yeong Park[1],
Su Jin Kim[1],
Myeongseob Lee[1],
Hae In Lee[1],
Ahreum Kwon[1],
Junghwan Suh[1],
Kyungchul Song[1],
Hyun Wook Chae[1],
Bonglim Joo[2],
Ho-Seong Kim[1]

[1]Department of Pediatrics, Division of Pediatric Endocrinology, Severance Children's Hospital, Endocrine Research Institute, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Pediatric Neurology, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea

Purpose: Patients with Turner syndrome (TS) have distinct neurocognitive and psychosocial characteristics. However, few clinical studies have reported neuropsychological findings in Korean patients. This study investigated the neurocognitive and psychosocial profiles of Korean children with TS.
Methods: This retrospective cross-sectional study analyzed 20 pediatric patients (<18 years) with TS at the Department of Pediatric Endocrinology at Yonsei University Severance Children's Hospital in South Korea from January 2016 to March 2019. We selected 20 age- and sex-matched controls from among those who visited the endocrinology clinic and were confirmed to have no clinical abnormalities. All participants underwent several neuropsychological tests.
Results: In the Korean Wechsler Intelligence Scale for Children-IV test, the Full-Scale Intelligence Quotient of the TS group was within the normal range. The Perceptual Reasoning Index, Working Memory Index, and Processing Speed Index scores were significantly lower in the TS group than in the control group. In contrast, the Verbal Comprehension Index did not differ significantly between the groups. The Comprehensive Attention Test results showed that the TS group displayed borderline visual selective attention. The social quotient score was significantly lower in the TS group than in the control group.
Conclusion: Pediatric patients with TS in Korea displayed distinct neurocognitive and psychosocial characteristics. Patients in the TS group maintained their verbal function, but their attention, visuospatial function, and social competence were low. Our findings will contribute to the development of education programs for patients with TS to improve their neurocognitive and psychosocial functioning.

Keywords: Turner syndrome, Neurocognitive phenotype, Psychosocial functioning, Child

Highlights

- This article highlights the neurocognitive and psychosocial characteristics in Korean patients with Turner syndrome. Patients with Turner syndrome maintained their verbal function, but attention, visuospatial function, and social competence were lower compared with normal controls.

Introduction

Turner syndrome (TS) is a relatively common genetic disorder caused by partial or complete loss of the X chromosome. The clinical features of TS include short stature, gonadal dysgenesis, various renal and cardiovascular defects, and specific psychosocial and neurocognitive profiles.[1,2] Despite some individual variation in TS severity, patients with TS present unique neurocognitive and psychosocial characteristics according to developmental period. During

Received: 14 September, 2022
Revised: 1 November, 2022
Accepted: 7 November, 2022

Address for correspondence:
Ho-Seong Kim
Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Email: kimho@yuhs.ac
https://orcid.org/0000-0003-1135-099X

ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

early infancy, some patients with TS exhibit a high rate of developmental delay across all domains of development, including fine motor, gross motor, and language skills.[3] The risk of neurodevelopmental delay increases following medical or surgical interventions. However, most patients with TS display relatively typical psychosocial development.[4] In early childhood, patients with TS manifest attention deficits, hyperactivity, and low social competence with obvious short stature.[4,5] As they grow, their neurocognitive and psychosocial development continues to diverge from that of their typically developing counterparts. Most children with TS manifest Full-Scale Intelligence Quotient (FSIQ) scores in the normal range, but they display relative strength in the verbal domains and weaknesses in domains such as arithmetic, visuospatial processing, and executive functioning.[6] In addition, patients with TS are at high risk for anxiety, depression, and attention-deficit hyperactivity disorder (ADHD).[7] Young adult patients with TS generally have normal self-perceived physical and mental health; however, some patients report social anxiety and reduced self-esteem and often complain of difficulties in relationships with colleagues.[8-10] In contrast with those findings, a population-based cohort study of 1,392 TS patients reported a relatively high risk of neurodevelopmental or psychiatric disorders, including intellectual disability, autism-spectrum disorder, eating disorders, behavioral and emotional disorders, and schizophrenia.[11]

Despite those previous findings, little research has examined the neurocognitive and psychosocial characteristics of children and adolescents with TS in Korea. Therefore, we evaluated the neurocognitive and psychosocial functions and quality of life (QoL) of pediatric Korean patients with TS.

Materials and methods

1. Participants

This retrospective cross-sectional study recruited pediatric patients (<18 years) with TS from the Department of Pediatric Endocrinology at Yonsei University Severance Children's Hospital in South Korea from January 2016 to March 2019. Twenty patients who were diagnosed with TS using a chromosome test and underwent neuropsychological tests were eligible for the study. We randomly selected 20 sex- and age-matched control participants from among patients who visited the endocrinology clinic to assess their health and growth status and were confirmed to be healthy and growing normally. Neuropsychological tests were administered to the controls after obtaining written consent from the parents/participants, as indicated. Patients with TS who received treatment or medications other than growth hormone or sex hormones, which are generally administered to TS patients, were excluded from the study. Moreover, we excluded children with chronic diseases or regular medications from the control group. The exclusion criteria for both groups were as follows: known history of IQ ≤70 or intellectual disability, history of brain injury, auditory impairment, and visual impairment.

2. Data collection

Demographic and clinical data were obtained from medical records: age, body weight, height, weight standard deviation score (SDS), height SDS, body mass index, karyotype, age at diagnosis, growth hormone therapy, estrogen therapy, and comorbid conditions.

3. Neurocognitive and psychosocial evaluation

Patients with TS and the controls underwent several neuropsychological tests to assess their intelligence, memory, attention, executive function, emotion, behavior, and adaptive function (Table 1).

1) Korean Wechsler Intelligence Scale for Children-IV and Korean Wechsler Primary and Preschool Scale Intelligence

For the intelligence evaluations, we used the Korean Wechsler Intelligence Scale for Children-IV (K-WISC-IV) and Korean Wechsler Primary and Preschool Scale Intelligence (K-WPPSI). Participants younger than 6 years were assessed for intelligence using the K-WPPSI, which consists of the FSIQ, Verbal Scale IQ, and Performance Scale IQ scales, with a mean of 100 and standard deviation (SD) of 15.[12] Participants 6 years and older were assessed for intelligence using the K-WISC-IV, which comprises 5 scales: FSIQ, Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI), with a mean of 100 and SD of 15.[13]

The VCI of the K-WISC-IV was used as a measure of verbal ability, such as understanding, learning, retaining verbal information, and using language to solve novel problems. The PRI of the K-WISC-IV was used as a measure of visuo-perceptual ability, such as understanding visual information and solving novel abstract visual problems. The WMI of the K-WISC-IV was used as a measure of a participant's ability to maintain verbal information in short-term memory and to manipulate that information, assessing attention, concentration,

Table 1. Neuropsychological tests and assessment tools

Classification	Test
Intelligence	K-WPPSI, K-WISC-IV
Memory	Rey-Kim Memory Test
Executive Function	Children's Color Trails Test (CCTT)
Attention	Comprehensive Attention test (CAT)
Behavior	Korean-Child Behavior Checklist (K-CBCL)
Adaptive Behavior	Social Maturity Scale (SMS) Pediatric Quality of Life Inventory (PedQL)
Emotion	Children's Depression Inventory (CDI) Self-Concept Inventory (SCI)

K-WPPSI, Korean Wechsler Primary and Preschool Scale Intelligence; K-WISC, Korean Wechsler Intelligence Scale for Children-IV.

and working memory. The PSI of the K-WISC-IV was used to measure the speed of mental and graphomotor processing.

2) Comprehensive Attention Test

We administered the Comprehensive Attention Test (CAT) to measure comprehensive attention, including visual and auditory attention. The attention quotient (AQ) was determined using the CAT. AQ scores ≤69, 70–84, and ≥85 indicate defect, borderline defect, and average, respectively.[14]

3) Rey-Kim Memory Test

We administered the Rey-Kim Memory Test (RKMT) to evaluate verbal and nonverbal memory performance. The participants learned 15 unrelated words and pictures over 5 trials and were requested to recall them immediately and 20 minutes later. The mean score of the memory quotient (MQ) was 100±15. The MQ comprises 10 indices, and the subscales have a mean score of 10±3.[15]

4) Children's Color Trails Test

The Children's Color Trails Test (CCTT) evaluates visual-motor coordination, attention, and cognitive impairment. The CCTT part 1 requires the participants to identify numbers in ascending order (1–2–3) and to connect them rapidly. In the CCTT part 2, the participants sequentially connect numbers while alternately connecting colors (pink-yellow-pink). The CCTT score is determined by the time (seconds) from the beginning of inspection to completion and the number of errors. The mean CCTT score was 50±10.[16]

5) Korean-Child Behavior Checklist

The Korean-Child Behavior Checklist (K-CBCL) test, completed by parents, was used to measure sociality, behavior, and adaptability. To provide estimates of behavioral problems, we examined the individual subscales of the K-CBCL and the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. For the behavioral problems and DSM criteria subscales, a higher score indicates more severe problems. We also evaluated total competence, social competence, and school competence, with higher scores indicating better performance.[17]

6) Social Maturity Scale

The Social Maturity Scale (SMS) was designed to measure the social competence of people 30 years of age or younger. The social age and social quotient were measured by conducting a test with 117 items. Higher social age and social quotient scores indicate greater social competence.[18]

7) Pediatric QoL Inventory

We administered the Pediatric QoL Inventory (PedQL) test, which consists of self-reported questionnaires, to measure QoL. The PedQL test consists of 23 questions about functioning in the physical, emotional, social, and school domains. The parents of those in the experimental group evaluated the QoL of their child. The scores range from 0 to 100, with a higher score indicating better QoL in children and adolescents.[19]

8) Children's Depression Inventory

The Children's Depression Inventory (CDI) is a self-reported test consisting of 27 items used to measure depressive thoughts and feelings. The scores range from 0 to 54, with higher scores indicating more depressive thoughts and feelings.[20]

4. Study outcomes

The primary outcome was difference in neurocognitive and psychosocial test scores between patients with TS and their sex- and age-matched healthy controls.

5. Statistical analysis

We performed the *t*-test, Wilcoxon rank-sum test, Fisher exact test, and chi-square test to evaluate differences between the TS group and control group. The Mann-Whitney *U*-test and Fisher exact test were used to evaluate differences between the abnormal score group and normal score group on the K-WISC-IV. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All data are expressed as mean±SD unless otherwise specified. A *P*-value ≤0.05 indicates a statistically significant difference between groups.

Table 2. Demographic and clinical characteristics of the participants

Variable	Patients with TS (n=20)	Controls (n=20)
Sex	All female	All female
Age at study (yr)	9.4±3.3	9.1±3.2
Height (cm)	124.0±18.6	128.7±20.8
Height SDS	-2.09±0.77	-0.81±0.90
Weight (kg)	30.3±11.7	29.8±12.0
Weight SDS	-1.06±1.20	-0.67±0.90
BMI (kg/m^2)	18.9±3.6	17.2±2.0
Age at diagnosis (yr)	6.5	-
Karyotype		
Mosaicism	15 (75)	-
45,X	5 (25)	-
Growth hormone treatment	20 (100)	-
Estrogen treatment	3 (15)	-
Comorbidity[†]	6 (30)	-

Values are presented as mean±standard deviation or number (%).
TS, Turner syndrome; SDS, standard deviation score; BMI, body mass index.
[†]Comorbidity: 1 patient with atrial septal defect repair and partial anomalous pulmonary venous return repair; 1 patient with eccentric aortic valve regurgitation and bicuspid valve; 1 patient with atrial septal defect; 1 patient with horseshoe kidney; 1 patient with scoliosis; 1 patient with hip dislocation surgery.

6. Ethical statement

This study was conducted with the approval of the Institutional Review Board of Severance Hospital (4-2020-0894). Written informed consent was obtained from all patients/parents.

Results

1. Clinical characteristics of participants

Table 2 summarizes the clinical data of all participants, who were female. The mean ages of the TS and control groups were 9.4±3.3 and 9.1±3.2 years, respectively. The mean heights of the TS and control groups were 124±18.6 cm and 128.7±20.8 cm, respectively. The height SD scores were -2.09±0.77 and -0.81±0.90 in the TS and control groups, respectively, revealing a low height SDS in the TS group. The mean body weights were 30.3±11.7 and 29.8±12.0 kg in the TS and control groups, respectively, with mean weight SD scores of -1.06±1.20 and -0.67±0.90. Body mass index values were 18.9±3.6 and 17.2±2.0 kg/m^2 in the TS and control groups, respectively, which were within the normal range. The chromosomal type was 45,X in 25% of the participants, and mosaicism was confirmed in 75% of the participants. All patients with TS (100%) were currently under growth hormone treatment. Three patients with TS (15%) were currently under estrogen treatment. Among the patients with TS, 6 (30%) had comorbid diseases or a medical history of surgery (1 patient with atrial septal defect repair and partial anomalous pulmonary venous return repair, 1 patient with eccentric aortic valve regurgitation and bicuspid valve, 1 patient with atrial septal defect, 1 patient with horseshoe kidney, 1 patient with scoliosis, and 1 patient with hip dislocation surgery).

2. K–WISC–IV and K–WPPSI

The TS group exhibited significantly lower FSIQ, PRI, WMI, and PSI scores than the control group (P<0.005, P<0.05, P<0.001, and P<0.005, respectively). The TS group presented an FSIQ score of 90.75±17.30, whereas the control group presented a score of 109.43±12.33. Within the TS group, 3 patients had borderline FSIQ (15%) and 2 patients had deficit FSIQ (10%). The TS group presented a WMI score of 83.31±17.27 and a PSI score of 89.75±12.78, which are within the low average range. In contrast, the VCI score did not differ significantly between the groups (Table 3). Among the subtests, the TS group displayed significantly lower scores for Block Design (P<0.05), Matrix Reasoning (P<0.05), and Picture Completion (P<0.05) in PRI; Digit Span (P<0.001), Letter-Number Sequencing (P<0.001), and arithmetic (P<0.05) in WMI; and Symbol Search (P<0.01) in PSI compared with the control group. Of the K-WISC-IV subtests in the TS group, the Picture Completion score was the lowest at 6.69±2.89, which indicated a borderline deficit.

We performed within-group *post hoc* analyses among the indices to compare index-level discrepancies. The TS group had higher a VCI score than PRI, WMI, and PSI scores (P<0.05, P<0.005, and P<0.05, respectively). No index-level discrepancies

Table 3. Korean Wechsler Intelligence Scale scores in children with TS compared with age-matched controls

Variable	Patients with TS (n=16)	Controls (n=16)	*P*-value
Full-scale IQ	90.75±17.30	109.43±12.33	0.002
Verbal Comprehension Index	103.00±19.27	107.43±12.14	0.465
Similarities	10.56±3.60	11.75±2.18	0.267
Vocabulary	10.94±3.77	11.63±2.28	0.392
Comprehension	10.00±3.97	10.19±2.54	0.875
Information	9.31±3.53	9.25±3.24	0.879
Perceptual Reasoning Index	91.19±18.76	106.07±16.57	0.029
Block Design	8.13±3.18	10.75±2.72	0.019
Picture Concepts	10.06±3.49	10.50±3.48	0.725
Matrix Reasoning	7.63±4.06	11.63±4.81	0.016
Picture Completion	6.69±2.89	8.56±2.22	0.049
Working Memory Index	83.31±17.27	109.86±9.89	<0.001
Digit Span	7.06±3.47	11.31±2.5	<0.001
Letter-Number Sequencing	7.13±3.07	11.56±2.42	<0.001
Arithmetic	8.50±3.76	11.38±2.42	0.015
Processing Speed Index	89.75±12.78	105.07±12.31	0.002
Coding	8.88±2.47	10.56±3.33	0.182
Symbol search	7.63±2.53	10.31±2.65	0.006

Values are presented as mean±standard deviation (SD).
TS, Turner syndrome; IQ, intelligence quotient.
Scaled scores were obtained using the age-based norms provided with each index (mean±SD: 100±15) and subscale (mean±SD: 10±3). Index scores (<69, deficit; 70–79, borderline; 80–89, low average; 90–109, average; 110–119, high average; and 120–129, superior). Subscale scores (<4, deficit; 5–6, borderline; 7–8, low average; 9–11, average; 12–13, high average; and 14–15, superior).

were observed in the control group.

Next, we compared clinical characteristics (chromosome type, age, treatment history, and comorbidity) between patients with deficit and borderline scores and patients with normal scores on the K-WISC-IV. We found no differences between the groups (Supplementary Table 1).

In the K-WPPSI test performed on participants aged 3–5 years, the groups did not differ significantly (TS patients, n=4; control, n=4) (data not shown).

3. Comprehensive Attention Test

The omission error, commission error, response time, and response time variability scores for visual selective responses were significantly lower in the TS group than the control group (P<0.005, P<0.001, P<0.05, and P<0.001, respectively) (Table 4). The auditory selective CAT scores did not differ significantly between the groups. The forward correct response and memory span scores were significantly lower in the TS group than the control group (P<0.005 and P<0.001, respectively). The average scores in the TS group were borderline for visual selective response time variability, visual selective response time, forward correct response, and forward memory span.

4. Rey–Kim Memory Test

The MQ scores did not differ significantly between the groups. The drawing score, which is a subscale of RKMT, was significantly lower in the TS group than the control group. The TS group displayed borderline drawing scores (Supplementary Table 2).

5. Children's Color Trails Test

The CCTT scores did not differ significantly between the groups. The mean CCTT scores of both groups were within the average range. The TS group displayed a relatively low CCTT 1 score tendency compared with the control group; however, the difference was not significant (P=0.102) (Supplementary Table 2).

6. Korean–Child Behavior Checklist

The mean CBCL scores in the TS group were within the normal range, but the total behavioral problem, withdrawn/depressed, and social problem scores were significantly higher in the TS group than the control group (P<0.05, P<0.005, and P<0.005, respectively) (Table 5). According to the DSM criteria, somatic problems scored significantly higher in the TS group than the control group (P<0.05). The ADHD scores did not differ significantly between the groups. In the TS group, the total competence and social competence scores were significantly lower than in the control group (P<0.05 and P<0.005, respectively). The proportion of the social competence scores in the clinical range was significantly higher in the TS group than the control group (TS, 31.25%; control, 0%, P<0.05, Fisher's exact test).

7. Social Maturity Scale

The SQ of the TS group was significantly lower than that of the control group (TS, 97.32±11.62; control, 111.68±7.06, P<0.001) (Supplementary Table 3).

8. Pediatric QoL Inventory

The PedQL scores of the children in the TS group did not differ significantly from those in the control group. The scores for social and school items evaluated by the parents of patients with TS were significantly lower than those in the control group (P<0.005 and P<0.005, respectively) (Supplementary Table 4).

Table 4. Comprehensive Attention Test scores in children with TS compared with age-matched controls

Attention quotient	Patients with TS (n=18)	Controls (n=18)	*P*-value
Omission error, visual selective	88.83±29.36	105.33±4.37	0.004
Commission error, visual selective	88.78±20.59	107.61±10.51	<0.001
Response time, visual selective	82.50±16.60	95.82±16.25	0.041
Response time variability, visual selective	72.89±27.09	103.00±14.29	<0.001
Omission error, auditory selective	107.39±29.21	111.33±11.95	0.849
Commission error, auditory selective	106.83±13.36	105.56±14.21	0.783
Response time, auditory selective	86.56±13.07	88.89±14.79	0.619
Response time variability, auditory selective	96.67±18.08	105.56±14.65	0.114
Forward correct response, working	77.73±16.92	104.00±13.71	0.002
Forward memory span, working	82.45±17.80	109.89±8.88	<0.001
Backward correct response, working	85.91±18.97	93.67±14.81	0.330
Backward memory span, working	89.27±22.12	97.11±11.27	0.424

Values are presented as mean±standard deviation.
TS, Turner syndrome.
Scaled scores were obtained using age-based neurocognitive test norms. T score (<69, deficit; 70–84, borderline; and >85, average).

Table 5. The Korean-Child Behavior Checklist score in children with TS compared with age-matched controls

Variable	Patients with TS (n=20)	Controls (n=20)	*P*-value
Behavioral problems			
Total behavior problems score†	54.5 (51.5, 65.5)	46.5 (38.0, 58.0)	0.023
Internalizing problems score†	56.0 (50.0, 64.0)	46.5 (37.0, 56.0)	0.054
Externalizing problems score†	57.0 (47.5, 65.5)	49.0 (42.0, 59.5)	0.228
Anxious/depressed‡	52.0 (50.0, 61.0)	50.0 (50.0, 59.0)	0.211
Withdrawn/depressed‡	56.0 (52.5, 63.0)	50.0 (50.0, 54.0)	0.005
Somatic complaints‡	54.5 (50.0, 64.0)	50.0 (50.0, 53.5)	0.051
Social problems‡	61.0 (56.0, 73.5)	50.0 (50.0, 55.5)	0.002
Thought problems‡	53.5 (50.0, 62.0)	51.5 (50.0, 53.0)	0.130
Attention problems‡	56.5 (50.5, 63.5)	50.0 (50.0, 59.5)	0.076
Rule-breaking behavior‡	56.0 (50.0, 61.0)	50.0 (50.0, 56.0)	0.162
Aggressive behavior‡	56.0 (50.0, 65.5)	50.0 (50.0, 59.0)	0.224
Other‡	55.0 (50.0, 63.5)	50.0 (50.0, 57.5)	0.214
DSM diagnostic criteria			
Affective problems‡	52.5 (50.0, 65.0)	50.0 (50.0, 59.0)	0.492
Anxiety problems‡	55.0 (50.0, 66.0)	50.0 (50.0, 57.0)	0.066
Somatic problems‡	53.0 (50.0, 62.0)	50.0 (50.0, 50.0)	0.025
ADHD problems‡	57.0 (53.0, 61.0)	52.0 (50.0, 66.0)	0.401
Oppositional defiant problems‡	56.0 (50.0, 61.0)	50.0 (50.0, 61.0)	0.300
Conduct problems‡	50.0 (50.0, 57.0)	50.0 (50.0, 57.0)	0.978
Competence			
Total competence§	43.0 (31.0, 51.5)	55.5 (45.0, 63.0)	0.014
Social competence‖	41.5 (30.0, 46.5)	55.0 (42.0, 65.0)	0.004
School competence‖	51.0 (45.5, 61.0)	53.0 (47.0, 61.0)	0.568

Values are presented as median (quartile 1, quartile 3).
TS, Turner syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders; ADHD, attention-deficit hyperactivity disorder.
Scaled scores were obtained using age-based neurocognitive test norms.
†T score (>64, clinical range; 60–63, subclinical range). ‡T score (>70, clinical range; 65–69, subclinical range). §T score (<36, clinical range; 37–40, subclinical range). ‖T score (<30, clinical range; 31–35, subclinical range).

9. Children's Depression Inventory

The mean scores for negative emotions self-reported on the CDI test did not differ significantly between the groups (TS, 7.40±6.36; control, 9.64±7.64, *P*=0.43, Wilcoxon rank-sum test) (data not shown).

Discussion

This study confirms the distinctive neurocognitive and psychosocial characteristics of Korean children with TS. In the K-WISC-IV test, the TS group displayed lower FSIQ scores than the control group, though the mean FSIQ score of the TS group was within the normal range. The pattern of global intellectual function was consistent with that reported in previous studies, suggesting that patients with TS do not commonly have global intellectual disabilities. However, patients with TS do maintain or display a slight decrease in FSIQ score compared with healthy controls.[21]

The between-group differences in individual indices of the K-WISC-IV reveal lower scores on all indices except the VCI score in the TS group compared with the control group. In addition, an analysis of within-group differences in the K-WISC-IV indices shows that the VCI score was highest among the subtests. In other words, nonverbal abilities are diminished in patients with TS, whereas verbal abilities are spared, consistent with the literature. The VCI scores of patients with TS remain within the normal range, demonstrating better maintained verbal abilities than nonverbal abilities.[5] Despite the maintenance of verbal function, verbal tasks requiring the substantial use of visuospatial function or executive function, such as sequence and temporal relationships, appear to be impaired in TS.[5]

Upon a closer examination of the individual K-WISC-IV indices, the PRI score was significantly lower in the TS group than in the control group, though it was within the normal range. All 4 PRI subtests displayed lower scores in the TS group than the control group, but all the results were within the normal range except the borderline Picture Completion score. The relatively low PRI score, which measures the ability to analyze and synthesize abstract visual problems and the ability to reason about nonverbal tasks, suggests that the TS group exhibits reduced ability to process visuospatial information. The impaired visuospatial function in patients with TS and the discrepancy between verbal and visuospatial abilities are

consistent with previous findings.[5] Some neuroimaging studies have suggested that visuospatial deficits are related to gray matter volume loss, including that in the right intra-parietal sulcus and superior parietal and postcentral gyri, in patients with TS.[22,23] Functional magnetic resonance imaging studies have demonstrated activation deficits in the parietal cortex.[24,25]

In our study, the TS group displayed a lower average WMI score than the control, and within-group *post hoc* analyses revealed that the WMI score was lower than the VCI score (P=0.002 by *post hoc* analysis). The lower WMI score, which measures attention, visual-motor coordination, concentration, and working memory, suggests that attention and working memory were impaired in the TS group. A previous study showed that patients with TS have low working memory and WMI scores.[6] In addition, the TS group demonstrated significantly lower arithmetic subtest scores than the control group. Poor math performance in the TS group is associated with poor visual tracking, visual-motor coordination, and figure-ground processing.[26]

In this study, the PSI score of the K-WISC-IV, used as a measure of mental and graphomotor processing speed, was lower in the TS group than in the controls. In other words, decreased cognitive functions such as visual-motor coordination, attention, and concentration in patients with TS could affect their PSI scores. In our study, chromosome type, growth hormone or estrogen treatment, and comorbid diseases did not affect the K-WISC-IV scores.

Together with the results of the K-WISC-IV, we speculate that children with TS have a normal range of global intellectual function but decreased visuospatial function that results in diminished attention, poor working memory, and decreased cognitive functions affecting execution. The verbal function was maintained in patients with TS; however, they displayed low attention, working memory, arithmetic skills, and visuospatial problem-solving ability, similar to the pattern seen in patients with nonverbal learning disability (NLD).[27,28]

Decreased visuospatial function in children with TS was also confirmed by CAT score, which revealed that visual selective attention, but not auditory selective attention, was lower in patients with TS. This finding suggests that a decrease in visuospatial function in TS might lead to the diminished attention observed in our and previous studies.[3,5,8] Attention is closely related to executive function.[29] Previous studies have reported low attention and impaired executive ability because of visuospatial difficulties in patients with TS.[5,7,30] Executive function in our patients with TS, as assessed by the CCTT, was not impaired. However, this finding cannot exclude the possibility of impaired executive function in TS. No definitive tests for executive function are available because it involves complex processes such as cognitive conversion, control, and inhibition.

Even though the K-CBCL scores assessing sociality, behavior, and adaptability were within the normal range in the TS group, total behavioral problems, withdrawal/depression, and social problems were prominent. The mean social competence score in patients with TS was within the normal range; nonetheless, 31.25% of the patients experienced difficulty in social relationships. According to the DSM diagnostic criteria, only the scores for somatic problems were significantly higher in the TS group than the control group, and even those were within the normal range. Unlike previous studies, we did not observe an association between TS and a high risk of ADHD.[3] However, we performed the K-CBCL test using a parental self-report about the possibility of ADHD. Additionally, no significant depression was observed in the TS group in our study. Children with TS have been reported to have high levels of depression and anxiety,[11,31,32] though other studies found no difference in depression.[33] In our study, children with TS might not have reported emotional problems because we included several patients who had not yet reached puberty. Patients with TS might recognize their emotional problems as they age; this possibility requires additional research and interpretation.

The SQ score on the SMS test was lower in the TS group than the control group. In this study, children with TS displayed lower social competence and social adaptation, consistent with earlier findings.[4,5] Impaired social competence is related to impaired facial cognition, poor performance in recognizing the expressions of anger and fear, and impaired eye gaze processing.[5]

Parental assessments of social and academic QoL were lower in the TS group than the control group. However, the QoL reported by participants did not differ between the groups.

The neurocognitive profiles of patients with TS were similar to those with NLD.[27] Similar to NLD treatment, education programs for children with TS should include social training and learning therapy to improve their neurocognitive function. Learning therapy requires a curriculum to improve visuospatial, attention, planning, and organizational skills. Moreover, additional math instruction and extended education time (to accommodate slower processing speed and attentional deficits) could help these children. Interpersonal and self-esteem training are also necessary social skills. Low social competence is related to impaired cognitive function; thus, education to improve cognitive and visuospatial functions should be combined to improve social competence. Furthermore, training for facial emotion recognition and interpretation of social cues might be helpful. An individualized education program specific to TS is required so patients can improve their psychosocial functioning, QoL, and neurocognitive function.

This study was conducted at a single center with an insufficient number of participants. Because of our small sample size, our results have limited generalizability. We intend to address this limitation in the future by increasing the number of patients. We did not collect or analyze data about socioeconomic status. The control group was selected from among healthy participants who visited a university hospital to evaluate their growth patterns. Therefore, selection bias, such as selecting a control group with a high socioeconomic level, might

have affected our results.

In summary, children with TS displayed normal global intellectual function and maintained good verbal function, but they exhibited reduced visuospatial function, attention, and social competence. Reduced attention, concentration, and social competence might result from attenuated visuospatial function. Our findings will allow physicians to focus on neurocognitive and psychosocial functioning when treating children with TS.

Notes

Supplementary Materials: Supplementary Tables 1-4 can be found via https://doi.org/10.6065/apem.2244222.111

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability: The data that support the findings of this study can be provided by the corresponding author upon reasonable request.

Acknowledgments: We thank clinical psychologists Da Sun Kim, Sae Mi Lee, and Sung Eun Choi and Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, for providing the neuropsychological tests and related information.

Author contribution: Conceptualization: SYP, HSK; Data curation: SYP, SJK, ML, HIL, AK, JS, KS, HWC, BJ, HSK; Formal analysis: SYP, SJK, ML, HIL, AK, JS, KS, HWC, BJ, HSK; Methodology: SYP, BJ, HSK; Project administration: SYP, HSK; Writing - original draft: SYP, BJ, HSK; Writing - review & editing: SYP, BJ, HSK

ORCID

Su Jin Kim: 0000-0003-0907-9213
Myeongseob Lee: 0000-0001-7055-3100
Hae In Lee: 0000-0002-7644-1617
Ahreum Kwon: 0000-0002-9692-2135
Junghwan Suh: 0000-0002-2092-2585
Kyungchul Song: 0000-0002-8497-5934
Hyun Wook Chae: 0000-0001-5016-8539
Ho-Seong Kim: 0000-0003-1135-099X

References

1. Ranke MB, Saenger P. Turner's syndrome. Lancet 2001;358:309-14.
2. Heo YJ, Jung HW, Lee YA, Shin CH, Yang SW. Arterial stiffness in young women with Turner syndrome using cardio-ankle vascular index. Ann Pediatr Endocrinol Metab 2019;24:158-63.
3. Hutaff-Lee C, Bennett E, Howell S, Tartaglia N. Clinical developmental, neuropsychological, and social-emotional features of Turner syndrome. Am J Med Genet C Semin Med Genet 2019;181:126-34.
4. Culen C, Ertl DA, Schubert K, Bartha-Doering L, Haeusler G. Care of girls and women with Turner syndrome: beyond growth and hormones. Endocr Connect 2017;6:39-51.
5. Hong D, Scaletta Kent J, Kesler S. Cognitive profile of Turner syndrome. Dev Disabil Res Rev 2009;15:270-8.
6. Mazzocco MM. The cognitive phenotype of Turner syndrome: specific learning disabilities. Int Congr Ser 2006;1298:83-92.
7. Green T, Shrestha SB, Chromik LC, Rutledge K, Pennington BF, Hong DS, et al. Elucidating X chromosome influences on attention deficit hyperactivity disorder and executive function. J Psychiatr Res 2015;68:217-25.
8. McCauley E, Feuillan P, Kushner H, Ross JL. Psychosocial development in adolescents with Turner syndrome. J Dev Behav Pediatr 2001;22:360-5.
9. Kiliç BG, Ergür AT, Ocal G. Depression, levels of anxiety and self-concept in girls with Turner's syndrome. J Pediatr Endocrinol Metab 2005;18:1111-7.
10. Lašaitė L, Krikščiūnienė R, Žilaitienė B, Verkauskienė R. Emotional state, cognitive functioning and quality of life of adult women with Turner syndrome in Lithuania. Growth Horm IGF Res 2019;45:37-42.
11. Avdic HB, Butwicka A, Nordenström A, Almqvist C, Nordenskjöld A, Engberg H, et al. Neurodevelopmental and psychiatric disorders in females with Turner syndrome: a population-based study. J Neurodev Disord 2021;13:51.
12. Kwak KC, Park HW, Kim CT. Korean Wechsler Primary and Preschool Scale for Children manual. 3rd ed. Seoul (Korea): Special Education Publishing Co., 1995.
13. Kwak GJ, Oh SH, Kim CT. Korean Wechsler Intelligence Scale for Children IV manual for experts. Seoul (Korea): Hakjisa, 2011.
14. Yoo HK, Lee JS, Kang SH, Park EH, Jung JS, Kim BN, et al. Standardization of the Comprehensive Attention Test for the Korean children and adolescents. J Korean Acad Child Adolesc Psychiatry 2009;20:68-75.
15. Kim HK. Assessment of memory disorders using Rey-Kim memory test. Korean J Rehabil Psychol 2001;8:29-48.
16. Shin MS, Koo HJ. Children's Color Trails Test. Seoul (Korea): Hakjisa, 2007.
17. Kim YA, Lee J, Moon SJ, Kim YJ, Oh KJ. Standardization study for the Korean version of the child behavior checklist for ages 1.5-5. Korean J Clin Psychol 2009;1:117-36.
18. Kim SK, Kim OG. Social Maturity Scale. Seoul: Chung-Ang Juksung, 2000.
19. Chung KM, Yang SK. A study for the standardization of the Korean Version of the Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales, self-report. Korean J Health Psychol 2012;17:677-95.
20. Kovacs M. Children's Depression Inventory manual. North Tonawanda, New York: Multi-Health Systems. Inc., 1992.
21. Waber DP. Neuropsychological aspects of Turner's syndrome. Dev Med Child Neurol 1979;21:58-70.
22. Molko N, Cachia A, Riviere D, Mangin J, Bruandet M, LeBihan D, et al. Brain anatomy in Turner syndrome:

evidence for impaired social and spatial–numerical networks. Cereb Cortex 2004;14:840-50.
23. Brown WE, Kesler SR, Eliez S, Warsofsky IS, Haberecht M, Reiss AL. A volumetric study of parietal lobe subregions in Turner syndrome. Dev Med Child Neurol 2004;46:607-9.
24. Haberecht MF, Menon V, Warsofsky IS, White CD, Dyer-Friedman J, Glover GH, et al. Functional neuroanatomy of visuo-spatial working memory in Turner syndrome. Hum Brain Mapp 2001;14:96-107.
25. Kesler SR, Haberecht MF, Menon V, Warsofsky IS, Dyer-Friedman J, Neely EK, et al. Functional neuroanatomy of spatial orientation processing in Turner syndrome. Cereb Cortex 2004;14:174-80.
26. Baker JM, Klabunde M, Jo B, Green T, Reiss AL. On the relationship between mathematics and visuospatial processing in Turner syndrome. J Psychiatr Res 2020;121:135-42.
27. Rourke BP, Ahmad SA, Collins DW, Hayman-Abello BA, Hayman-Abello SE, Warriner EM. Child clinical/pediatric neuropsychology: some recent advances. Annu Rev Psychol 2002;53:309-39.
28. Mammarella IC, Cornoldi C. An analysis of the criteria used to diagnose children with Nonverbal Learning Disability (NLD). Child Neuropsychol 2014;20:255-80.
29. Diamond A. Executive functions. Annu Rev Psychol 2013;64:135-68.
30. Lepage JF, Dunkin B, Hong DS, Reiss AL. Contribution of executive functions to visuospatial difficulties in prepubertal girls with Turner syndrome. Dev Neuropsycol 2011;36:988-1002.
31. Rickert VI, Hassed SJ, Hendon AE, Cunniff C. The effects of peer ridicule on depression and self-image among adolescent females with Turner syndrome. J Adolesc Health 1996;19:34-8.
32. Skuse D, Elgar K, Morris E. Quality of life in Turner syndrome is related to chromosomal constitution: implications for genetic counselling and management. Acta Paediatr Suppl 1999;88:110-3.
33. van Pareren YK, Duivenvoorden HJ, Slijper FM, Koot HM, Drop SL, de Muinck Keizer-Schrama SM. Psychosocial functioning after discontinuation of long-term growth hormone treatment in girls with Turner syndrome. Horm Res 2005;63:238-44.