Cognitive Profile of Children with Williams Syndrome: Comparison with Children with Prader-Willi Syndrome and Down Syndrome

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Purpose: The objectives were to examine following 2 questions related to cognitive profile for the children with Williams syndrome (WS); 1) Is there a significant advantage for verbal IQ over performance IQ in WS?; 2) Is there selective impairment in visuospatial ability in the children with WS?
Materials and Methods: Five children with WS with the age of 90.86±20.73 months were compared with 12 children with Prader-Willi syndrome (PWS) or Down syndrome (DS) with comparable age and IQ.
Results: All 5 children with WS showed intellectual disability whose mean scaled scores were 15.71±9.27 in verbal subtests and 14.29±7.50 in performance subtests, which did not show significant difference. There was no significant difference in the total sum of scaled scores of verbal subtests among WS, PWS and DS. There was no selective impairment in subtests which represented visuospatial tasks for the children with WS. However, the scaled score of object assembly was significantly lower in WS (2.29±0.95) compared to that of PWS (4.75±2.77; $P<0.05$).
Conclusion: The general notion that the children with WS would be relatively strong in verbal function when compared with their overall cognitive function was not observed in this study. The verbal function of the children with WS was not better when compared to the children with DS or PWS. There was no selective impairment of visuospatial function in the children with WS at this age. However, the visuospatial function was significantly low in the children with WS only when compared to the children with PWS.

Key Words: Williams syndrome, Prader-Willi syndrome, Down syndrome, Mental retardation

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Introduction

Intellectual disability or mental retardation is characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills, which originates before the age of 18[1)]. Williams syndrome (WS; OMIM #194050) is one of the genomic disorders

associated with intellectual disability[2]. The prevalence of WS has been reported to be approximately 1/7,500 birth to 1/20,000 births[3, 4], and is known to be caused by haploinsufficiency of chromosome 7q11.23[4-7]. The disorder is characterized by a multi-system involvement[6], and the major physiologic features include typical elfin facial appearance, frequent infantile hypercalcemia, cardiovascular problems such as supravalvular aortic stenosis and hypertension, and frequent hyperacusis[4-6, 8]. The developmental delay of cognition, motor and language is universal in WS, and intellectual disability is ultimately diagnosed in the majority of individuals with WS.

The most interesting psychological profiles of WS are significant weakness of visuospatial cognition and relative strength in language. In terms of visuospatial cognition, the persons with WS have been reported to be incapable of putting together the simple puzzles, owing to their inability to visualize an object as a set of parts[2, 4, 9-18]. This weakness has been suggested to be related with functional deficits of dorsal visual stream[5, 10, 19]. Regarding the language ability, a number of studies have shown that individuals with WS have a superior linguistic profile compared to their non-verbal abilities[10, 15, 18, 20, 21], however, the evidence remains inconclusive[21]. In fact, there are some controversies over the cognitive profile of children with WS. Some studies found a significant advantage for verbal IQ over performance IQ, while other studies revealed a non-significant trend in this direction[2, 4, 21, 22].

To the best of our knowledge, there are no reports either on the cognitive profile of children with WS or comparison of the cognitive profile of WS with other genetically determined intellectual disabilities in Korea. Therefore, the objectives of this study were to examine the following 2 questions; 1) Is there a significant advantage of verbal IQ over performance IQ in children with WS? and 2) Is there a selective impairment in visuospatial ability in children with WS?

Materials and Methods

1. Subjects

1) Children with WS

From August 1994 to July 2006, 13 children were diagnosed as WS at the laboratory of Department of Medical Genetics, Ajou University Medical Center. WS were confirmed by the positive fluorescent in situ hybridization test (FISH) for ELN (*elastin*) at chromosome 7q11.23[6]. Among the 13 children, 5 children who were included in this study were tested with either Korean Wechsler Intelligence Scale for Children-III (K-WISC-III) or Korean Wechsler Preschool and Primary Scale of Intelligence (K-WPPSI). Since remaining 8 children were too young to take the above 2 tests, they took Bailey Scales of Infant Development-II or Kauffman Battery for Children for the evaluation of cognitive function, therefore, they were not included in this study. The subjects of WS were 2 boys and 3 girls with the age of 90.86±20.73 months (range; 68-123 months old; Table 1). Case 3 and 4 underwent K-WPPSI twice; therefore, 7 tests done by 5 children with WS were included in this study.

2) Children with Prader-Willi syndrome (PWS) or Down syndrome (DS)

As comparison groups, the children with PWS or children with DS were selected based on following rationales; 1) PWS and DS are well known genetic causes of intellectual disabilities; 2) Regarding verbal function, DS is known to show relatively low expressive language function compared with their overall cognitive function [23-26], whereas PWS is known to have no deficiency of verbal function compared to their overall cognitive function[22, 27]; 3) In terms of visuospatial function, PWS is known to be proficient in putting together jigsaw puzzles[27, 28], whereas DS is known to have no deficiency or proficiency in visuospatial ability.

(1) Children with PWS

From August 1994 to July 2006, 18 children were diagnosed as PWS at the laboratory of Department of Medical Genetics, Ajou University Medical Center. PWS was confirmed by the FISH, microsatellite analysis and/or methylation-specific polymerase chain reaction. Among 18 children with PWS, 5 children who were tested with either K-WISC-III or K-WPPSI were included, and one child among them had the test done three times and one child went through the test twice. Therefore, 8 tests taken by 5 children with PWS were included in this study. They were 4 boys and one girl with the age of 81.75±15.25 months (range; 55-108 months old; Table 1). Three children had paternally derived microdeletion of 15q11-13, and 2 children had maternal disomy of 15q11-13.

(2) Children with DS

From August 1994 to July 2006, 124 children with DS visited the Department of Physical Medicine and Rehabilitation, Ajou University Medical Center. The majority of children with DS were too young to take K-WISC-III or K-WPPSI, and 7 children who took one of the above psychological tests were included in this study. They were 3 boys and 4 girls with the age of 91.71±29.64 months (range; 65-141 months old; Table 1). Their karyotypes were trisomy 21, and there was no translocation or mosaicism among these 7 children.

2. Evaluation of psychological profiles

We retrospectively reviewed the psychological reports (K-WISC-III, K-WPPSI) of these 17 children. Twenty two tests for 17 children were done by the same experienced psychologist from August 1994 to July 2006.

The K-WISC-III is the Korean version of WISC-III and evaluates intellectual abilities for the children at the age of 6 to 17 years, while the K-WPPSI is the Korean version of WPPSI and assesses intellectual functioning for the children at the age of 3-7 years old. The K-WISC-III/K-WPPSI consists of two parts; the verbal scale and the performance scale. Each of the verbal and the performance scales has 6 subtests. Among these 12 subtests, 6 subtests are included in both the K-WISC-III and the K-WPPSI; information, comprehension and arithmetic in verbal subtests; object assembly, block design and picture completion in performance subtests. The raw scores of each subtest of K-WISC-III/K-WPPSI were converted into the scaled scores which had 10 as mean and 3 as standard deviation in order to compare subtests and to obtain the intelligence quotient. IQ scores (total IQ, verbal IQ and performance IQ) which had 100 as mean and 15 as standard deviation were converted from the sum of the scaled score of each subtest. The K-WISC-III/K-WPPSI do not provide numeric full scale IQ in the case of IQ<50/IQ<35, respectively. Therefore, we used scaled scores for statistical analysis instead of IQ scores. The data on the total scaled score of 6 verbal subtests, the total score of 6 performance subtests, and the scaled scores of 6 subtests which were included in both the K-WISC-III and the K-WPPSI, were collected for analysis.

3. Statistical analysis

ANOVA tests for the comparison of cognitive profiles

Table 1. The Demographic Data of the Children According to Syndrome

Characteristics	Williams syndrome	Prader-Willi syndrome (n=5, 8 tests)	Down syndrome (n=7, 7 tests)
Gender (boy:girl)*	2:3	4:1	3:4
Age* (month-old;range)	90.86±20.73 (68-123)	81.75±15.25 (55-108)	91.71±29.64 (65-141)
K-WISC-III/K-WPPSI†	3/4	3/5	2/5

*No significant difference in age and gender among syndromes ($P > 0.05$)
†Korean Educational Development Institute-Wechsler Intelligence Scale for Children III/Korean Wechsler Preschool and Primary Scale of Intelligence

for the children with WS, PWS and DS and independent t-test for the comparison of scaled scores between verbal subtests and performance subtest within each syndrome were conducted. Chi-square test and ANOVA tests were used for the comparison of age and gender among syndromes.

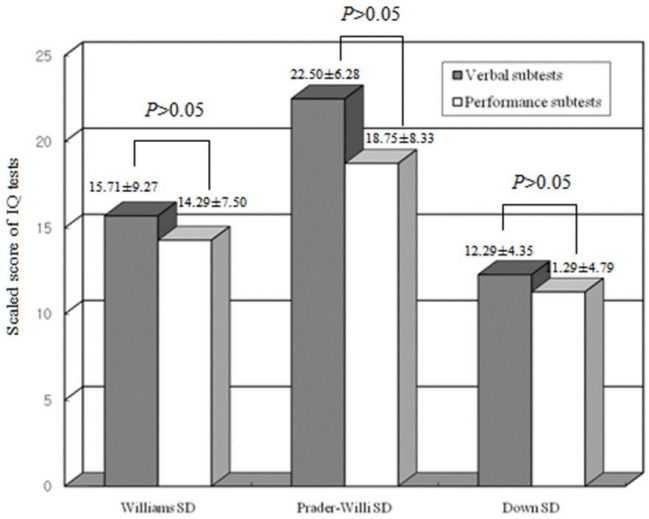

Fig. 1. Comparison of the scaled scores of verbal and performance subtests according to syndrome.

Results

The demographic data of the children according to syndrome are shown in Table 1. As seen in the table 1, there was no significant difference in age and gender according to syndrome (P>0.05).

All 5 children with WS showed intellectual disability of mean scaled scores 15.71±9.27 in verbal subtests and 14.29±7.50 in performance subtests, showing no significant difference (P>0.05; Fig. 1). Similar to the children with WS, the children with PWS and DS did not show any significant difference in the scaled scores between the verbal subtests and the performance subtest (P>0.05; Fig. 1). The total sum of scaled scores of verbal subtests for PWS was highest (22.50±6.28) and lowest in DS (12.29±4.35). However, there was no significant difference in the total sum of scaled scores of verbal subtests among WS, PWS and DS (P>0.05).

There was no significant difference in scaled scores among 6 subtests, especially in object assembly and

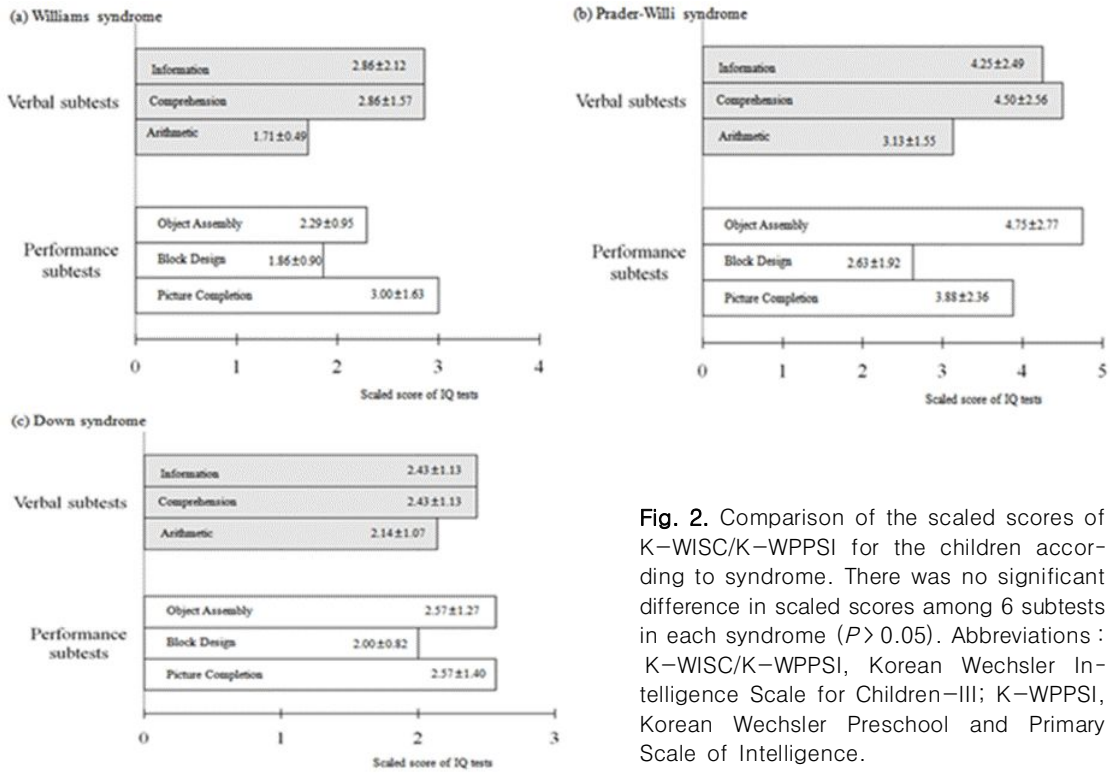

Fig. 2. Comparison of the scaled scores of K-WISC/K-WPPSI for the children according to syndrome. There was no significant difference in scaled scores among 6 subtests in each syndrome (P > 0.05). Abbreviations : K-WISC/K-WPPSI, Korean Wechsler Intelligence Scale for Children-III; K-WPPSI, Korean Wechsler Preschool and Primary Scale of Intelligence.

block design which represent visuospatial perceptual tasks for the children with WS (P>0.05; Fig. 2) as well as the children with PWS and DS (P>0.05).

However, the comparison of psychological profiles according to syndrome showed significant difference in the scaled score of object assembly among 3 syndromes (Fig. 3), and the post hoc test revealed that the scaled score of object assembly was significantly lower in WS (2.29±0.95) than that of PWS (4.75±2.77; P<0.05).

Taking all these findings together, we could not find either any significant advantages of the verbal IQ over the performance IQ or selective impairment in visuospatial ability in the children with WS at this age. However, there was significant weakness in visuospatial ability for the children with WS when compared to the children with PWS.

Discussion

Since British physician J.C. Williams and German cardiologist A. J. Beuren independently described the syndrome in 1961-1962, intellectual disability has been reported in the majority of individuals with WS. Williams Syndrome Critical Region (WSCR) at 7q11.23 is flanked by low copy repeats that predispose to nonallelic homologous recombination, ending up with the deletion of a number of genes found in WS. While the WS phenotype is the result of haploinsufficiency for a number of genes, the characteristic cognitive profile of WS is known to be related with a couple of genes. The deletion of the *GTF2IRD1* (general transcription factor IIi repeat domain containing 1) and/or *GTF2I* (general transcription factor IIi) genes located on the telomeric side of the critical region appears to be responsible for intellectual disability in WS[4, 12]. Furthermore, the deletion of *LIMK1* (lim kinase 1) in WSCR has also been implicated in the abnormality of visuospatial constructive cognition in WS[7]. In general, the visual cortex is divided into the ventral stream and the dorsal stream. The ventral stream is associated with object recognition and form representation, which is connected to the areas of the inferior temporal lobe. The dorsal stream stretches from the primary visual cortex in the occipital lobe into the parietal lobe, and is involved in spatial awareness and guidance of actions. Ventral stream processing, as measured with fMRI during passive viewing of pictures, attention demanding process of the identities of pictures and a shape-matching task, has been shown to be intact in WS, whereas dorsal stream function with participants attending the spatial locations of the same picture or performing a two-dimensional analogue of the classic block design task is found to be abnormal. With these functional deficits of dorsal visual stream, it is difficult for those with WS to perform visuospatial function as well as to judge distance and negotiate stairs[5].

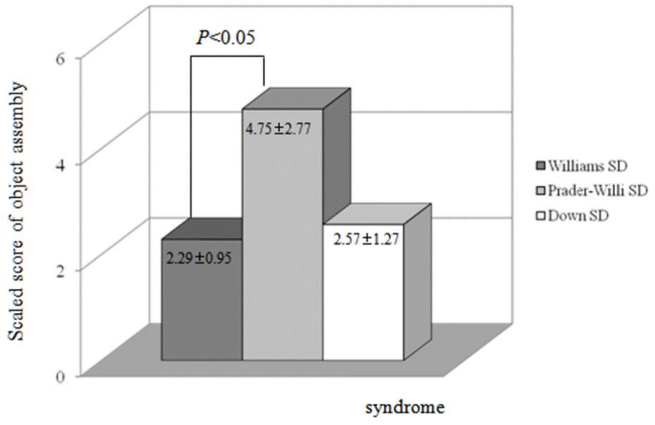

Fig. 3. Comparison of the scaled scores of object assembly subtest among three syndromes.

WS is characterized by a rare fractionation of higher cortical functioning, showing selective preservation of certain complex faculties (language, music, face processing, and sociability) in contrast to marked and severe deficits in other cognitive domains (reasoning, spatial ability, motor coordination, arithmetic, problem solving)[4, 29]. The characteristic cognitive profile of WS includes relatively good verbal skills alongside very deficient visuospatial abilities, unlike many others with learning difficulty[2, 4, 15, 18, 29]. The so-called cognitive-language dissociation of people with WS means signifi-

cant strength in verbal communication which exceeds their cognitive function[19]. According to the traditional Piagetian view, language acquisition is predicated on cognitive development. However, in 1989, Thal et al. reported the cases of three children with WS, who preceded language that was complex in terms of morphological and syntactic structures despite the fact that they lacked the supposed cognitive prerequisites[15]. Since this pioneering work, WS has frequently been cited as the evidence that language is independent of cognition[2]. There have been some speculations that linguistic competence may, to some extent, be the result of conversational strategies which enable them to compensate for various cognitive and linguistic deficits with a considerable degree of success[30]. In fact, overfriendliness and empathetic nature which have often been reported in WS has been thought to be helpful in terms of pragmatic verbal function of the children with WS. However, despite earlier reports that emphasized a strong social interest and empathy in WS, individuals with WS were reported to have pragmatic language impairments, poor social relationships and restricted interests. In some way, at least some individuals with WS would seem to share many of the characteristics of autistic disorder[23]. It is certain that the emergence of language is severely delayed in WS, but there is no evidence to suggest that this delay is any greater than what is expected on the basis of general cognitive delay[2]. Recent studies on language and face recognition in younger individuals with WS showed that all aspects of the language for WS show a delay and/or deviance throughout the development[31, 32]. When infants and toddlers with WS were tested alongside their Down syndrome counterparts, they appeared to be even delayed in vocabulary, despite outstripping them later in the adulthood[19]. Furthermore, Pagon et al. administered the WISC battery to individuals with WS and found no verbal advantage[13], whereas Udwin and Yule who administered the same battery reported a marginal but still statistically significant verbal advantage[18].

In the present study, the general notion that the children with WS are relatively strong in verbal function compared with their overall cognitive function has not been observed. Furthermore, we could not find any selective impairment in visuospatial ability compared to other subtests within each child with WS. In our present study, the deficit of visuospatial cognition for the children with WS was apparent only when compared to the age- and IQ-matched children with PWS. The children with WS showed almost half the scores on object assembly when tested alongside the children with PWS ($P<0.05$; 2.29 for WS, 4.75 for PWS). One of possible explanations for these negative results could be relatively young age of the subjects with the mean age of 90 month-old. There have been few reports on developmental trajectory of on cognitive profiles of young children with WS. Vicari et al. reported that the neuropsychological profile of younger children is different from those of the older children, indicating that initial states of the system cannot be inferred by the final state[33]. Therefore, it is possible for the children with WS to show typical cognitive profiles such as selective impairment of visuospatial function as they grow up, compared to other cognitive domains. Several limitations are noted in our current study, mainly due to its retrospective nature and relatively small number of subjects. Regardless of these limitations, however, it is believed that this is the first report on the psychological profiles of the children with WS. Therefore, the results described are expected to help building psychological profiles of the children with WS.

국문초록

목 적 : 윌리암스증후군 아동의 인지와 관련된 두 가지 특성을 검증하고자 하였다; 윌리암스증후군 아동은 언어성 지능이 동작성 지능 보다 유의하게 높다; 윌리암스증후군 아동은 시공간기능의 선택적 저하를 보인다.

대상 및 방법 : 평균연령 90.86±20.73개월의 5명의 윌리암스 증후군 아동의 인지적 특성을 연령 및 성별이 유사한

12명의 프라더윌리증후군 혹은 다운증후군 아동의 인지적 특성과 비교, 분석하였다.

결 과: 윌리암스증후군 아동에서 언어성 지능 항목의 합은 15.71±9.27, 동작성 지능 항목의 합은 14.29±7.50으로, 언어성 지능과 동작성 지능 간의 유의한 차이를 보이지 않았다. 윌리암스증후군, 프라더윌리증후군, 다운증후군 아동들 간의 언어성 지능의 유의한 차이는 관찰되지 않았다. 윌리암스증후군 아동에서 시공간지각과 관여된 세부항목의 선택적 저하는 관찰되지 않았으나, 물체조합 항목에서 프라더윌리증후군 아동에 비하여 유의한 기능의 저하를 보였다.

결 론: 윌리암스증후군 아동이 전체 지능에 비하여 상대적으로 높은 언어성 지능을 보인다는 일반적인 개념은 본 연구에서는 관찰되지 않았다. 동시에 윌리암스증후군 아동은 프라더윌리증후군이나 다운증후군 아동과의 비교 시에도 우수한 언어기능을 보이지 않았다. 그러나 윌리암스증후군 아동은 프라더윌리증후군 아동과 비교 시 현저히 낮은 시공간기능을 보였다.

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