Applied Neuropsychology: Child

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hapc20

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To cite this article: Cintia Michelle Domínguez-García, Carlos Alberto Serrano-Juárez, Mario Rodríguez-Camacho, Julieta Moreno-Villagómez, María Antonieta Araujo Solís & Belén Prieto-Corona (2022): Neuropsychological intervention in attention and visuospatial skills in two patients with Williams syndrome with different types of genetic deletion, Applied Neuropsychology: Child, DOI: 10.1080/21622965.2022.2063723

To link to this article: https://doi.org/10.1080/21622965.2022.2063723

Published online: 27 Apr 2022.

APPLIED NEUROPSYCHOLOGY: CHILD
https://doi.org/10.1080/21622965.2022.2063723

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CASE REPORT

Neuropsychological intervention in attention and visuospatial skills in two patients with Williams syndrome with different types of genetic deletion

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ABSTRACT

Williams Syndrome (WS) is a neurodevelopmental disorder with a distinctive physical, cognitive, and behavioral profile caused by a microdeletion in the q11.23 region of chromosome 7. The neuropsychological profile of WS is characterized by intellectual disability, hypersociability, and deficits, especially in attention and visuospatial skills. Our objective was to assess the effectiveness of a neuropsychological intervention program in attention and visuospatial skills in two patients with WS (aged 7 and 13 years old) with different types of deletion (1.5 and 1.8 Mb). Cognitive, behavioral, and adaptive abilities were evaluated through various neuropsychological tests and scales; the neuropsychological intervention program was subsequently applied, and we assessed its effectiveness. Both patients initially presented significant deficits in attention and visuospatial skills. After the program, we found improvements in attention and visuospatial skills. In addition, both patients had significant clinical advances and changes in adaptive behaviors (social and self-care). These findings suggest that this intervention program could improve attention processes, visuospatial skills, and some aspects of adaptive behavior in patients with WS, regardless of deletion size. Although the sample was small, limiting the generalizability of the results, we believe this program could be a helpful resource for professionals working with individuals with WS.

KEYWORDS

Attention; neuropsychological intervention; neuropsychology; visuospatial skills; Williams syndrome

Introduction

Williams syndrome (WS) is a microdeletion disorder that occurs in as many as 1:7500 individuals, caused by the loss of the WS critical region (WSCR) on chromosome 7q11.23. The loss of the genes in this region affects multiple systems, making WS a disorder with cardinal features including cardiovascular disease (stenosis of the great arteries and supravalvular aortic stenosis), particular craniofacial features, and a specific behavioral and cognitive profile including intellectual disability, hypersociability, significant alterations in visuospatial skills (Shalev et al., 2019; Van Herwegen, 2015), deficits in attention and executive functioning (Shalev et al., 2019; Vivanti et al., 2017), difficulty in recognizing emotions in facial expressions (Ibernon et al., 2018), and other features (Kozel et al., 2021).

Most people with WS (91–95% of cases) have a 1.5 megabase (Mb) deletion, which encompasses 25–27 genes and is considered typical (Serrano-Juárez et al., 2018), with the remainder having a slightly larger deletion. While most deletions range from 1.55Mb to 1.83Mb, there are rare individuals with deletions that encompass smaller or larger segments of the WSCR, often with one common and one unique breakpoint. In addition, some present larger deletions that extend beyond the WSCR and result in additional features (Kozel et al., 2021).

Animal models have been used to identify the contribution of individual genes to the complex phenotype of WS. According to Kopp et al. (2019), mouse models are particularly suitable because a region on mouse chromosome five is syntenic to WSCR; models can thus include a mouse line with a complete deletion of the WSCR genes that shows behavioral disruptions and altered neuronal morphology. These models also allow manipulation of the mouse genome to delete targeted subsets of genes in the locus. Large numbers of animals can be bred with identical partial mutations, enabling statistical analyses to overcome variable expressivity, among other advantages.

The genes on which mouse models of the WS phenotype have most commonly focused are *BAZ1B*, *VPS37D*, *STX1A*, *LIMK1*, *CLIP2*, *GTF2IRD1*, *GTF2I*, and *ELN* (Kopp et al., 2019). *ELN* has shown the greatest evidence for a role in the phenotypic consequences of WS since the loss-of-function point mutations or intragenic deletions within this gene are associated with familial supravalvular aortic stenosis and develop cardiovascular manifestations that are indistinguishable from those found in WS (Osborne, 2010).

Several mouse models for the cognitive and behavioral characteristics of WS have suggested that the loss of *GTF2I*

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(which is lost in a typical deletion) is a major contributor to intellectual disability and social disinhibition (Kozel et al., 2021), and it has also been related to visuospatial deficits, hyperacusis, and craniofacial characteristics of WS (Chailangkarn et al., 2018). These models have also shown that the deletion of *GTF2IRD1*, another frequently lost gene, likely contributes to difficulties in social communication (Kozel et al., 2021).

Serrano-Juárez et al. (2018) also showed that children with WS who present an atypical deletion of 1.8Mb lack two additional genes, including *GTF2IRD2*, which is suspected of causing a major deficit in the areas of visuospatial functioning, social reasoning, and cognitive flexibility, as well as a greater prevalence of obsessive behaviors. According to Porter et al. (2012), given the regulatory influence of *GTF2IRD2* on *GTF2IRD1*, the loss of the former may lead to structural alterations in sites where the latter is normally expressed, leading to deeper deficits in visuospatial and social skills.

Although mouse models are powerful and essential tools to shed light on the complex correlations between genotype and phenotype in WS, and on the development and testing of therapeutics, they are not a perfect match to human disease outcomes, especially in the case of cognitive conditions, since mouse behavior does not precisely correspond to human behavior. The information garnered from these studies must therefore be interpreted carefully for clinical practice (Kopp et al., 2019; Kozel et al., 2021).

Despite a growing number of studies focusing on the cognitive and behavioral characteristics of individuals with WS and their genetic correlations, the literature regarding specific interventions for WS is sparse. The few published studies of interventions focus mostly on language (Diez-Itza et al., 2017; Martínez-Castilla et al., 2019), music therapy (Weiss et al., 2021), techniques for managing anxiety (Phillips & Klein-Tasman, 2009), or on general recommendations (Dykens, 2001).

Even though deficits in visuospatial abilities and attention have been reported in the literature as commonly found in the neuropsychological profile of WS, with an acknowledgment of their role in the acquisition of literacy, the development of arithmetic skills, and activities in daily life (Foti et al., 2020), there have been few studies focused on interventions related to these processes.

The objective of the current study was thus to evaluate the effectiveness of a neuropsychological intervention program addressing attention and visuospatial skills in two patients with WS with different genetic deletions (1.5 and 1.8 Mb). The hypothesis was that the intervention would improve their attentional and visuospatial abilities and that these changes would be different, depending on the genes involved in the deletion.

Method

Participants

Fourteen persons with WS were contacted based on information provided by the Asociación Mexicana de Síndrome de Williams A.C. Of these, three agreed to participate, and only two male patients finished the intervention program. Patient 1 was aged 7 years 1 month and Patient 2 was aged 13 years 5 months at the time of the pre-intervention assessment. A geneticist clinically evaluated both patients, and a blood sample was obtained for chromosome microarray analysis. Both patients resided in Mexico City.

According to their parents and medical histories, both patients required an incubator at birth and had delayed development milestones; they also were frequently ill with respiratory diseases and had asthma. Patient 1 was born with a heart murmur, which was treated with medication. The two patients presented similar socioeconomic and stimulation conditions: middle class, with previous stimulation in psychomotor skills and academic accommodations. They were distinguished mainly by genetic deletion and age.

Assessment instruments

Wechsler Intelligence Scale for preschool and primary level (WPPSI III; Wechsler, 2011)

This instrument was applied to assess functioning in general cognitive domains and obtain a reliable measure of the full-scale intelligence quotient (FSIQ).

Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2007)

This instrument was used to assess functioning in general cognitive domains and obtain a measure of the FSIQ for Patient 2.

NEUROPSI attention and memory (Ostrosky-Solís et al., 2012)

This instrument is designed to assess attention and memory modalities, including working memory and short- and long-term memory with verbal and visuospatial material, as well as executive functioning, in persons aged 6–85. Only the subtests related to attention and memory were used in the current study.

Frostig Developmental Test of visual perception (DTVP-3; Hammill et al., 2016)

This test assesses the presence and degree of visual and visual-motor perception difficulties in persons aged 4–13.

Children's and adolescents' evaluation system (SENA; Fernández-Pinto et al., 2015)

This instrument is used to detect emotional and behavioral problems in persons aged 3–18 (internalized, externalized, contextual, and specific problems). It also explores areas of vulnerability and the presence of personal resources acting as protective factors that can be used in the intervention.

Adaptive behavior assessment system (ABAS II; Harrison & Oakland, 2013)

This instrument assesses adaptive behavior from birth to 89 years of age. Its objective is to provide a complete assessment of a person's daily functional abilities in different areas or contexts to determine whether they can function in their daily lives without requiring help from others.

Chromosome microarray analysis (CMA; Adam et al., 2021)

This method of genetic analysis is used to detect copy number variants (loss or gain of chromosomal material). With a greater sensitivity than the traditional karyotype, it detects large and small copy number variants. Depending on the method used, CMA may involve scanning the entire genome (cytogenetic CMA), targeting regions of the genome, or targeting a specific chromosome or chromosome segment.

Procedure

An information session about the project was held with parents and patients before starting the pre-intervention assessment. The parents of the patients provided written informed consent, and the project was approved by the university ethics committee as adhering to the Declaration of Helsinki. A semi-structured interview was subsequently conducted to learn the clinical history of each patient. Patients were then given neurological and genetic evaluations, and a CMA was performed to determine the deletion size. The neuropsychologist in charge of the assessment and intervention did not know the results of these evaluations until the post-intervention evaluations of both patients had been completed; this was the only blinding possible under the conditions of this study. The pre-intervention neuropsychology assessment was made, followed by the neuropsychological intervention in attention and visuospatial skills. The activities of the program used different stimuli and procedures than those used for the assessment. The intervention program consisted of 28 sessions, twice a week, lasting from 60 to 90 min. Both patients completed all 28 sessions. Because of the COVID-19 pandemic, sessions 11–28 and the post-intervention assessment for Patient 1 were carried out with teleneuropsychology.

Neuropsychological intervention program addressing attention and visuospatial skills

The program was based on two models. For attention, it used the clinical model of Sohlberg and Mateer (2001), which establishes the components of attention in a hierarchical design (focused, sustained, selective, alternating, and divided attention) that analyzes performance considering the different elements of the tasks. Based on the performance of the patients, more activities were designed for selective attention, and some of them were based on the premises of Attention Process Training (APT), using verbal stimuli (animal and object names and sounds) and visual stimuli (letters and numbers presented on a laptop screen). Given the exploratory nature of the intervention and the characteristics of the patients, these activities did not strictly follow the APT manual (see Table 1).

For visuospatial skills, the intervention used Frostig's model of visual perception (Frostig, 1972; Hammill et al., 2016), which considers five areas of visual perception (eye-hand coordination, figure-ground, constancy of shape, position in space, and spatial relationships) as necessary for the development of children's academic skills (reading, writing, and calculation) and adaptive skills (see Table 1).

Statistical analysis

The Reliable Change Index (RCI) was used to compare the performance of each participant before and after the intervention, with correction for learning effects (LE) using the standard error of the Iverson difference (RCI + LE) (Duff, 2012; Iverson, 2001). The resulting RCI + LE is compared with a typical distribution table; 1.64 is considered the cutoff for a statistically significant change.

Results

Genetic results

The results of the chromosome microarray analysis (see Figure 1) showed that Patient 1 presented a typical deletion of 1.5 Mb and Patient 2 a 1.8Mb deletion, lacking the *GTF2IRD2* gene.

Neuropsychological results

Patient 1 (1.5 Mb deletion)

Patient 1 obtained an FSIQ of 70 (WPPSI III), indicating borderline performance on tasks related to perceptual processing, visual abstraction, and processing speed (performance and verbal IQ), with a verbal IQ in the lower average range, indicating better performance on verbal tasks. A significant clinical change ($p \leq 0.05$) was found after the intervention in the visual detection and memory recognition subtests of the NEUROPSI: Attention and Memory tests, in the copying and form constancy subtests, and in the three DTVP-3 indexes: visual-motor integration, motor-reduced visual perception and general visual perception (Table 2).

Significant clinical changes were found after the intervention in the social and self-care areas of the ABAS-II ($p \leq 0.05$), in the global problems index, and on the depression and rigidity scales of the SENA ($p \leq 0.05$) (Table 3).

Patient 2 (1.8 Mb deletion)

Patient 2 obtained an FSIQ of 55 (WISC-IV). His expressive language was fluent and grammatically correct most of the time, and his understanding was adequate, but with deficiencies in verbal abstraction. His lowest score was on the working memory index (WMI), representing the ability to learn and retain information in memory and use it immediately. Like Patient 1, he presented greater deficiencies in

Table 1. Activities and compensatory strategies of the neuropsychological intervention program.

Processes	Theoretical models	Activities	Compensatory strategies or practical exercises
Attention	Sohlberg and Mateer model (Sohlberg & Mateer, 2001) • Sustained attention • Selective attention	• Cancelation • Cancelation with distractors • Search for stimuli • Find the differences • Alphabet soup	• Finger tracking • Visual tracking from top to bottom, from left to right • Self-instruction strategy
Visuospatial skills	Frostig model (Frostig, 2013), exercises based on "Figures and Shapes: Program of Visual Perception and Preschool Readiness: Corporal, Object and Graphic." • Body scheme • Body image • Body concept • Visuomotor coordination • Figure background • Perceptual constancy • Position in space • Spatial relations	• Identify and name parts of the body in oneself, in others, and in drawings • Lateralization exercises • Analysis of shapes and patterns in relation to one's own body and space • Hand-eye coordination exercises • Identification of geometric figures • Recognition of figures in a specific background • Recognition of central aspects of figures or shapes when they appear in different sizes, colors, shapes, textures, and positions • Distinguishing inversion and rotation of figures • Copying of figures	• Play "Simon says" to identify and name parts of the body and lateralization • Play "rooster, hen, chick" to calculate how many steps are needed to reach certain objects or places • Highlight geometric figures • Join points to form geometric figures • Find and name objects with shapes of geometric figures in the environment • Identify the central aspects of figures or drawings • Distinguish different sizes • Self-instruction strategy

Note. Each activity and compensatory strategy was based on a theoretical model.

Figure 1. Schematic representation of the genes lost in a typical and atypical deletion in Williams syndrome. *Note.* Schematic representation of the genes lost in the typical group with the conserved *GTF2IRD2* gene (1.5 Mb deletion) (A) corresponding to Patient 1, and in the atypical group without *GTF2IRD2* (1.8 Mb deletion) (B), corresponding to Patient 2.

Table 2. Results of the reliable change index (RCI) and learning effect (LE) for the NEUROPSI and DTVP-3, patient 1.

	Score			
Index/subtest/process	Pre	Post	Cutoff	RCI + LE
NEUROPSI: attention and memory				
Attention				
Digit progression	1	4	6.84	1.58
Visual detection	1	10	8.8	4.74**
Digit detection	1	1	5.5	0
Working memory				
Digit regression	4	4	5.84	0
Coding				
Memory curve	11	14	7.76	1.58
Memory				
Spontaneous memory	11	14	6.71	1.58
Key memory	14	14	7.05	0
Memory (recognition)	1	14	8.21	6.85**
DTVP-3				
Visuomotor integration	73	94	78.8	2.21**
Eye-hand coordination	7	6	4.53	−0.53
Copying	4	12	6.42	4.22**
Motor-reduced visual perception	54	71	79.35	1.79**
Figure-ground	2	4	5.36	1.05
Visual closure	5	5	4.69	0
Constancy of form	1	7	7.11	3.16**
General visual perception (5 subtests)	61	81	78.03	2.11**

Note. Shows the results of the RCI + LE analysis of Patient 1 (1.5Mb deletion). Cutoff point 1.64. **RCI exceeds the cutoff for what is considered a significant clinical change ($p \leq 0.05$).

Table 3. Results of the ABAS-II and SENA, patient 1.

	Score			
Index/area	Pre	Post	Cutoff	RCI + LE
ABAS-II area				
Communication	3	4	6.56	0.53
Academic skills	1	1	4.90	0
Self-direction	5	4	7.79	−0.53
Leisure	2	3	8.22	0.53
Social	5	9	8.69	2.11**
Use of community resources	5	4	6.90	−0.53
Home life	7	9	8.82	1.05
Health and safety	5	6	7.78	0.53
Self-care	4	8	7.21	2.11**
Index				
Conceptual	63	63	78.36	0
Social	68	79	90.47	1.64**
Practical	71	79	83.83	1.19
General adaptive behavior	64	70	82.25	1.26
SENA				
Global index				
Global problem index	68	60	52.93	−1.69**
Emotional problem Index	57	50	51.40	−1.48
Behavioral problem index	64	60	52.55	−0.84
Executive function problem index	76	69	53.91	−1.48
Personal resource index	48	48	47.44	0
Problem scales				
Internalized problems				
Depression	61	47	51.40	−2.21**
Anxiety	66	60	53.29	−0.95
Social anxiety	38	45	45.24	1.11
Somatic complaints	56	47	52.98	−1.42
Externalized problems				
Attention problems	76	70	55.79	−0.95
Hyperactivity-impulsivity	74	70	53.74	−0.63
Anger management problems	63	59	52.28	−0.63
Aggression	69	61	52.70	−1.26
Defiant behavior	54	55	51.92	0.16
Other problems				
Unusual behavior	91	97	56.56	0.95
Vulnerability scales				
Emotional regulation problems	69	72	52.54	0.47
Rigidity	58	45	50.48	−2.06**
Isolation	62	56	54.39	−0.95
Personal resource scales				
Integration and social competence	58	52	47.61	−0.95
Emotional intelligence	58	58	50.76	0
Willingness to study	30	36	46.33	0.95

Note. Table shows the results of the analysis of the reliable change index (RCI) + learning effects (LE), Patient 1. Cutoff point 1.64. **RCI exceeds the cutoff for what is considered a significant clinical change ($p \leq 0.05$). The SENA personal resource index and integration and social competence scale categories of emotional intelligence and willingness to study are scored inversely.

tasks related to visuospatial analysis (block design), visual-motor coordination (processing speed), and vocabulary. Significant clinical changes were found after the intervention in the digit detection and memory recognition subtest of the NEUROPSI: Attention and Memory test ($p \leq 0.05$) and in the Visual-motor Integration Index of the DTVP-3 ($p \leq 0.05$) (Table 4).

Significant clinical changes were found after the intervention in the areas of academic skills, self-direction, leisure, social, use of community resources, homelife, and self-care on the three ABAS-II indexes (conceptual, social, and practical) and in general adaptive behavior ($p \leq 0.05$) (Table 5).

Discussion

The objective of this study was to evaluate the effectiveness of a neuropsychological intervention program focused on attention processes and visuospatial skills in two patients with WS with gene deletions of differing sizes. Although the sample was small ($N = 2$) and the results thus have little statistical power, we believe that the findings obtained provide valuable ideas for those who work with this population.

Table 4. Results of the RCI and LE for the NEUROPSI and DTVP-3, patient 2.

	Score			
Index/subtest/process	Pre	Post	Cutoff	RCI + LE
NEUROPSI: attention and memory				
Attention				
Digit progression	5	4	7.78	−0.53
Visual detection	1	1	7.91	0
Digit detection	1	9	6.25	4.22**
Working memory				
Digit regression	7	7	4.46	0
Coding				
Memory curve	7	4	9.23	−1.58
Memory				
Spontaneous memory	6	4	7.66	−1.05
Key memory	3	6	7.35	1.58
Memory (recognition)	11	7	7.05	−2.11
DTVP-3				
Visuomotor integration	73	88	82.36	2.24**
Eye-hand coordination	7	9	5.74	1.05
Copying	4	7	6.62	1.58
Motor-reduced visual perception	50	56	75.64	0.89
Figure-ground	2	5	5.92	1.58
Visual closure	3	4	3.70	0.53
Constancy of form	2	4	7.73	1.05
General visual perception (5 subtests)	60	69	73.02	1.34

Note. Table shows the results for Patient 2 (1.8 Mb deletion). Cutoff point 1.64. **RCI exceeds the cutoff for what is considered a significant clinical change ($p \leq 0.05$).

Neuropsychological findings of the patients

Patient 1 (1.5 Mb deletion, age 7 years 1 month)

This patient's FSIQ of 70 indicated performance below that expected for his age, and a score of 64 on the general adaptive behavior index of the ABAS-II, which places him in a deficient functioning range compared to the normative sample. He has marked difficulty in the daily handling of abstract concepts and particular weakness in academic skills and in skills necessary to establish interpersonal relationships, with specific difficulties in those abilities required to meet basic needs and participate in society, although he shows strength in his relationships at home.

Patient 2 (1.8 Mb deletion, age 13 years 5 months)

This patient's FSIQ of 55 indicates a performance much lower than expected according to his age and education, and his score of 56 on the general adaptive behavior index of the ABAS-II indicates significant difficulties in the daily management of abstract and academic concepts, in skills required to establish interpersonal relationships, and in skills necessary to meet basic needs and participate in society. He has strengths, however, in relationships at home and in health and safety.

Both patients presented significant deficits in visuospatial skills, attention problems reflected in neuropsychological tasks and scales, and strengths in linguistic skills, specifically expressive language, though with difficulties in verbal

Table 5. Results of the ABAS-II and SENA ICC of patient 2.

	Score			
Index/area	Pre	Post	Cutoff	RCI + LE
ABAS-II				
Communication	1	4	5.37	1.58
Academic skills	1	5	3.62	2.11**
Self-direction	1	9	6.13	4.22**
Leisure	1	8	5.77	3.69**
Social	1	7	7.36	3.16**
Use of community resources	1	5	6.75	2.11**
Home life	4	11	8.47	3.69**
Health and safety	5	5	6.39	0
Self-care	2	6	4.75	2.11**
Index				
Conceptual	54	78	71.80	3.58**
Social	51	86	82.25	5.22**
Practical	58	79	75.61	3.13**
General adaptive behavior	56	79	75.17	4.85**
SENA				
Global index				
Global problem index	50	55	52.03	3.58**
Emotional problem index	48	57	49.49	1.34
Behavioral problem index	48	45	51.76	−0.45
Executive function problem index	53	58	55.16	0.75
Personal resource index	35	39	42.36	0.60
Problem scales				
Internalized problems				
Depression	54	63	50.99	1.42
Anxiety	41	52	51.87	1.74**
Social anxiety	42	45	47.21	0.47
Somatic complaints	58	61	49.07	0.47
Externalized problems				
Attention problems	64	66	57.77	0.32
Hyperactivity-impulsivity	54	57	54.39	0.47
Anger management problems	45	45	49.75	0
Aggression	48	43	52.27	−0.79
Defiant behavior	47	47	53.33	0
Other problems				
Unusual behavior	48	47	55.56	−0.16
Vulnerability scales				
Emotional regulation problems	45	48	52.01	0.47
Rigidity	46	54	51.15	1.26
Isolation	59	79	64.84	3.16**
Personal resource scales				
Integration and social competence	40	34	44.26	−0.95
Emotional intelligence	36	55	39.73	3.00**
Willingness to study	39	36	43.98	−0.47

Note. Table shows the results of the analysis of the reliable change index (RCI) + learning effects (LE), Patient 2. Cutoff point 1.64. **RCI exceeds the cutoff for what is considered a significant clinical change ($p \leq 0.05$). The SENA personal resource index and integration and social competence scale categories of emotional intelligence and willingness to study are scored inversely.

comprehension and speech. These findings are consistent with most descriptions of the neuropsychological profile of WS (Atkinson & Braddick, 2012; Bellugi et al., 1994; Brun et al., 2001; Farran et al., 2003; Karmiloff-Smith, 2012; Martens et al., 2008; Pober, 2010; Rhodes et al., 2010; Semel & Rosner, 2003; Shalev et al., 2019; Sotillo et al., 2007; Van Herwegen, 2015).

Patient 2 presented greater difficulties in learning new information than Patient 1. Both patients achieved better performance through verbal repetition and recognition cues, which could be related to the hypothesis that short-term phonological memory is preserved in people with WS (Grant et al., 1997). However, there are some studies that question this assumption (Majerus et al., 2003).

Both patients presented deficits in the recognition and management of laterality, observed in the game "Simon says" and in other activities, consistent with Chasouris et al. (2014), who suggest that children with WS present atypical laterality. Similarly, both patients presented difficulty in distinguishing between the letters *d* and *b*, in addition to problems in literacy reported by their parents.

Both patients performed better on perceptual tasks, such as the copy subtest of Rey's complex figure test (Figures 2 and 3) and the visuospatial skills exercises. They identified some isolated components of the figures, ruling out severe deficits in visuoconstruction, but consistent with the interpretation that people with WS cannot appreciate the figures globally, since they do not identify the spatial relationships between the elements to create a drawing or a model (Serrano-Juárez et al., 2018; Heiz & Barisnikov, 2016).

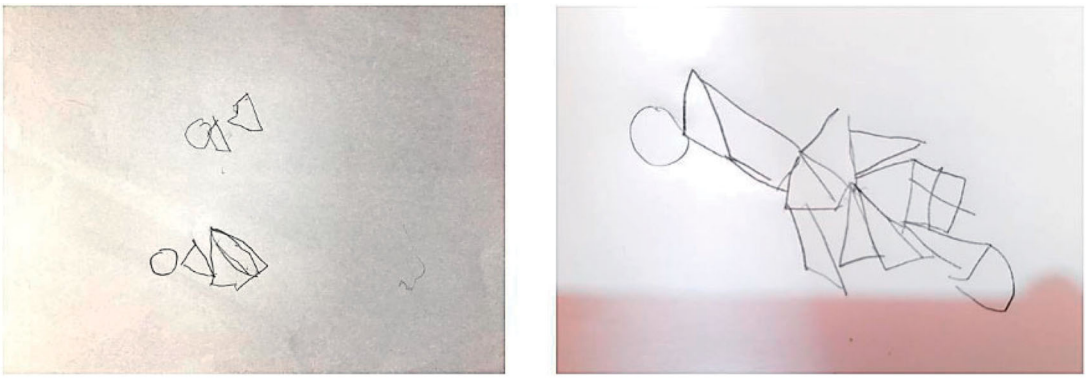
Neuropsychological intervention

Improvements were found in some attentional components and visuospatial skills after the intervention, especially visual-motor integration. Clinically significant changes were found in digit detection, which evaluates sustained and selective verbal attention, in Patient 2, and in visual detection, which evaluates sustained and selective visual attention, in Patient 1, who also showed improvement in components of verbal memory.

Both patients showed similar performance in the pre-intervention assessment in DTVP-3. However, Patient 1, with typical deletion (1.5 Mb), seems to have benefited more from the intervention program by presenting clinically significant changes in all the DVTP-3 indexes, while Patient 2, with an atypical deletion (1.8 Mb), showed clinically significant changes in only one of the indexes. These findings support the idea that the absence of the *GTF2IRD1* and *GTF2I* genes could contribute to a more substantial impact on deficits in visuospatial processes (Chailangkarn et al., 2018; Hirota et al., 2003; Porter et al., 2012; Serrano-Juárez et al., 2018). Porter et al. (2012) argue that these deficits are due to the loss of *GTF2IRD2*, which can generate structural alterations in brain sites where *GTF2IRD1* is expressed, leading to more profound alterations in visuospatial abilities.

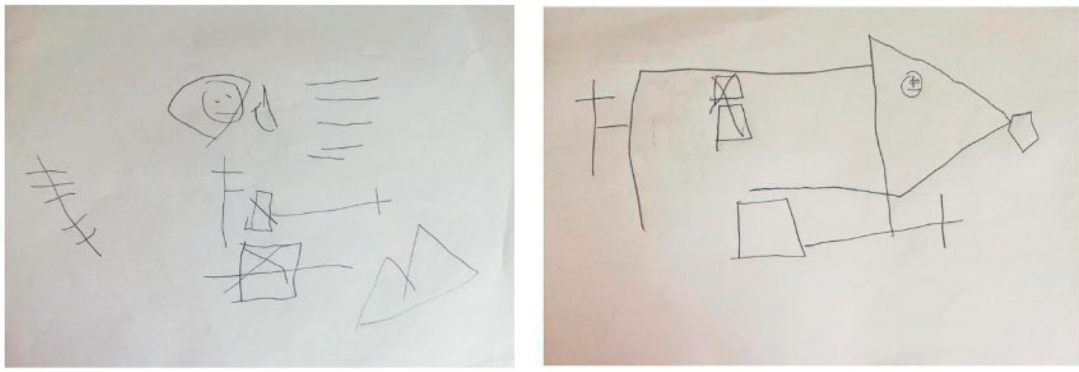
Behavioral and emotional aspects

We found no significant clinical changes or improvements related to emotional and behavioral problems in Patient 1 after the intervention. Patient 2 showed an increase in behavioral and executive function issues, anxiety, and isolation, which to a certain extent could be due to the lockdown conditions of the COVID-19 pandemic and the change in school from face-to-face to online classes. However, both patients presented significant clinical improvements in adaptive behaviors, such as social and self-care. Patient 2 showed improvement in most of the evaluated areas. According to the scales applied, Patient 1 presented signs of anxiety (constant hand and foot movements, sweaty hands, and a nervous attitude), which coincides with the description of anxiety symptoms reported in the literature for people with WS (Bellugi et al., 1999; Lacruz-Rengel et al., 2015; Morris, 2010; Pober, 2010; Royston et al., 2017; Van Herwegen, 2015). Overall, the intervention had an impact on both



Pre-intervention assessment, May 5, 2020 Post-intervention assessment, Agust 2, 2020

Figure 2. Comparison of performance copying the semi-complex figure, pre- and post-intervention, Patient 1.



Pre-intervention assessment, September 9, 2019 Post-intervention assessment, March 3, 2020

Figure 3. Comparison of performance copying the Rey-Osterreith complex figure, pre- and post-intervention, Patient 2.

adaptive behavior and the psychological development process of the patients.

Other factors to consider

The age difference between the patients may also have influenced their performance. Patient 2 turned 14 during the intervention and qualitatively showed greater willingness and attention to instructions during the sessions. Patient 1, 7 years old, needed more social reinforcers and attractive material to keep his attention on the activities. This difference could be explained by the development of the attentional processes of the two patients: attentional circuits continue to develop between 6 and 12 years of age, and from 7 to 9 years there is an increase in sustained attention (Hapering, 1996 as cited in Pérez). From 9 to 12, attentional control processes mature, causing an improvement in selective attention (Goldberg et al., 2001 as cited in Pérez). Based on these considerations and on the characteristics of the activities and strategies of this program, the age at which the implementation of this program could be more beneficial is during early school years and older (Heim & Keil, 2012), since children at that age probably have the necessary attentional circuits.

Considerations regarding the use of teleneuropsychology

For the teleneuropsychology sessions, one of the parents was asked to be present during the entire session to supervise the patient. Sessions were conducted in a distraction-free environment, and the internet connection was stable. The activities that involved tools or physical materials were adapted to a digital version.

In recent decades the modality of interventions has expanded to include telerehabilitation, or teleintervention, a system that uses technology to benefit patients and clinicians, minimizing the barriers of distance, time, and cost (Noogle et al., 2013). Teleneuropsychology refers to neuropsychological assessment and intervention through remote contact with the patient, usually through videoconferencing techniques. The administration of neuropsychological tests generally follows the instructions of standardized tasks, adapting them to the video medium without losing sight of the cognitive processes. Research on videoconferencing interventions has generally revealed that face-to-face intervention and videoconferencing methods are comparable (Smith, 2017).

Harder et al. (2020) examined neuropsychological evaluations of children conducted online from home and observed no significant differences in the results obtained in person

and in videoconferencing, or in the participants' performance during sessions. In their study, participants and caregivers were satisfied with the videoconference format, and they conclude that online evaluations are valid and present results comparable to those obtained with a traditional face-to-face evaluation. Likewise, Smith (2017) notes that studies exploring psychological interventions using videoconferencing have generally found that face-to-face intervention and videoconferencing methods are comparable. However, there are limitations in evaluation and intervention using videoconferencing. These include distractions at home (Harder et al., 2020) and technical problems, from the availability of equipment to the speed and quality of the internet connection. The continued need for such technologies may help to increase their availability and quality (Myers & Turvey, 2012). Additional study of these questions will be needed to ensure that the results of these modalities are truly comparable.

Limitations

This study found favorable results in a neuropsychological intervention program to improve attention and visuospatial skills in people with WS, but it has certain limitations. Although we had the support of the National Association of Williams Syndrome Mexico in contacting prospective participants, the sample recruited was small. A larger number of participants could better support the findings. Another significant limitation was the lack of blinding in the second evaluation; future studies should include this control. Because of the COVID-19 pandemic, it was necessary to adapt the intervention and final assessment with videoconferencing, which may also have affected the results. Finally, we have compared two patients with different size deletions. Although Patient 2 (1.8 Mb deletion) seemed to benefit less from the intervention in visuospatial skills than Patient 1 (1.5 Mb deletion), ideally we would compare the performance of Patient 2 with that of another patient with the same deletion, for a more rigorous comparison of the effects of the intervention.

Conclusion

The objective of this study was to evaluate the effectiveness of a neuropsychological intervention program focused on attention processes and visuospatial skills in two patients with WS with different types of genetic deletion. We found that the program improved sustained and selective attention and visuospatial skills, especially in visual-motor integration, and also the adaptive behavior of both patients. Patient 1, with the typical deletion, benefited more from the intervention program. The use of visual tracking strategies in cancelation exercises can help improve selective and sustained attention, and the self-instruction strategy is helpful with internalizing instructions. The establishment of a strategy to identify the elements and relationships between skills could be beneficial for the development of visual-motor integration, facilitating the ability to draw and copy figures and the development of writing in children with WS. It is possible that the use of these strategies, combined with pedagogical techniques, could help individuals with WS improve their academic skills. The elements of this neuropsychological intervention program can also be adapted to meet the needs of individual patients.

Acknowledgments

Programa de Apoyo de Proyectos de Investigación e Innovación Tecnológica (PAPIIT) DGAPA-UNAM IN308719 de la Universidad Nacional Autónoma de México. BECAS NACIONALES DE CONACYT CVU 926999 de Cintia Michelle Domínguez-García.

Disclosure statement

The authors report there are no competing interests to declare.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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