Original article

Cognitive functioning in Williams Syndrome: A study in Portuguese and Spanish patients

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ABSTRACT

Williams Syndrome (WS) is a genetic neurodevelopmental disorder caused by a submicroscopic deletion on chromosome 7 q11.23. This is a systemic disorder in which cardiac problems and mental retardation are the key phenotypic symptoms. Although displaying a general cognitive impairment, they are most often described as exhibiting a peak and valley profile, with relative sparing of language and face processing abilities and severe impairment of visual–spatial cognition. In this study, we conducted a detailed cognitive assessment using Wechsler Intelligence Scales on a WS and a normal development control group. To explore the hypothesis of a dissociative cognitive architecture in WS, performance on subtests, factorial indexes and composite measures of Verbal, Performance and Full Scale Intelligence Quotient were analysed. Individuals with WS were found to score in Full Scale Intelligence Quotient (FSIQ) within mild to moderate mental retardation interval, and had significantly lower scores in all measures when they were compared with the normal development group. However, a specific intragroup cognitive profile was found for Williams Syndrome (confirming Mervis' definition of the WS cognitive profile) along with a specific developmental pathway (absence of an age-associated cognitive decline).

1. Introduction

Williams Syndrome (WS) is a neurodevelopmental disorder, with a prevalence of 1 in 7500,[30] characterized by a submicroscopic deletion on chromosome 7 q11.23.[20] This genetic syndrome was first described by Williams and collaborators[36] who recognized a group of 4 children with supravalvular aortic stenosis, typical facial features and mental retardation. The WS patients have an unusual phenotype, which includes a distinctive profile of physical, medical, neuropsychological, neuroanatomic and neurological characteristics.[3,4,8,11,12,21,24] Their typical physical characteristics include facial dysmorphology,

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specific clinical phenotype, poor motor coordination, muscle tone disorders (hypertonia) and articulation problems.[24] WS individuals display also distinct behavioural patterns, characterized by an excessive social behaviour, with a strong impulse towards social contact and affective expression.[2,18]

Intellectual disability is a feature of WS genetic disorder,[37] and descriptions of a consistent deficit of global intellectual functioning in this syndrome are reported.[4,7,14,16,31] In addition, several studies using a variety of standardized measures (e.g., Wechsler Intelligence Scales, Kaufman Brief Intelligence Test – K-BIT, Stanford Intelligence Scales and Differential Ability Scales – DAS) point out a high prevalence of mental retardation, within the mild to moderate interval.[4] In a variety of IQ tasks, participants with WS score in the interval ranging from 55 to 69[5,7,14–16,22,26,31,33] with standard global scores between 40 and 90.[4] Additionally, IQ seems to remain stable during adulthood, with no evidence of age-associated cognitive decline.[16,26,32]

Although global intellectual impairment is a consistent result, there is some debate on Williams Syndrome literature concerning the excellence of verbal over non-verbal measures. Thus, some studies found evidence for a superiority of verbal over non-verbal measures,[16,17] including longitudinal evidence that verbal abilities develop faster than non-verbal ones.[17] This characteristic pattern of cognitive functioning, described in children with WS, persists also in adulthood, where the Performance IQ remains inferior to Verbal IQ.[16] Nevertheless, this dissociative pattern within WS cognition has been questioned, with other studies reporting the absence of significant discrepancies between linguistic and non-linguistic abilities in these patients.[7,15]

Of note, a consistent result emerging from previous studies is that most of the individuals with WS exhibit some intellectual impairment, with children and adults scoring in mild mental retardation interval in standardized intelligence tests. However, this overall IQ score may hide the existence of unique cognitive profile with specific performance in some subtests[23,25] and the operationalization of WS Cognitive Profile (WSCP) has been proposed.[23] This profile considers the level of performance in central subtests (measure of global intellectual ability) and performance in 4 specific tests: Digit Recall, Naming/Definitions, Similarities and Pattern Construction, suggesting that WS patient's performance in the latter test is lower with respect to the other tests.

In light of the several discrepancies in previous studies assessing the cognitive profile of subjects with WS, we thought of interest to provide a detailed analysis of cognitive functioning in Portuguese and Spanish participants with WS and in an age-matched control group with normal development, using Wechsler Intelligence Scales. The objective was to test the existence of a specific intragroup cognitive profile and its developmental stability in WS.

2. Method

Two groups of participants took part in this study. Seventeen participants with WS diagnosis (11 female and 6 male individuals), with age ranging from 7 to 31 years ($M = 17.35$, $SD = 6.74$), were recruited at Instituto de Genética Médica

Prof. Jacinto de Magalhães (Porto, Portugal) ($n = 13$) and Fundación Xenómica Pública Galega (Santiago de Compostela, Spain) ($n = 4$), with previously confirmed positive fluorescent in situ hybridization (FISH) to elastin gene deletion in chromosome 7.[20] Exclusion criteria were the presence of any sensorial or speech disorder, as well as comorbility with severe psychopathology not associated with the syndrome. Control group was composed of normal developing individuals, without history of sensorial, psychiatry or neurodevelopmental disorder. This group was matched with WS group on gender, age ($M = 17.74$, $SD = 6.69$), education ($Mdn = 9$) and socio-economical status ($Mdn = 4$).

2.1. Instruments

Wechsler Intelligence Scales – WISC-III[35] and WAIS-III[34] were used to assess general cognitive functioning in patients with ages inferior to 16 years and older, respectively. This scale is one of the most used international system in assessing Intellectual Quotient (Full Scale IQ – FSIQ) allowing the discrimination of two intellectual levels related to verbal and non-verbal abilities (Verbal IQ – VIQ and Performance IQ – PIQ), factorial indexes and performance in different subtests. In addition, it is an instrument that has been widely used in assessing mental retardation, including WS.

Due to previous reports with evidence of psychometric differences between WISC-R and WAIS-R,[28,29] specially when we analyse IQ levels in the lower range (higher FSIQ is associated with WAIS-R), a separate analysis was performed for children and adult groups (differences between VIQ and PIQ).

2.2. Procedure

After explaining the goals of the research, socio-demographic, diagnosis, clinical story and consent form elements were obtained. Then, Wechsler Intelligence Scale (3rd revision) was administered to both groups.

2.3. Data analysis

Descriptive analysis and frequencies were used to characterize both groups of participants. Normality and variance homogeneity criteria were tested for all dependent variables with Kolmogorov–Smirnov and Shapiro Wilk's tests. Parametric t tests were used to compare the groups and paired t tests were used to analyse intragroup variables. Association between age and Full Scale IQ was evaluated using Pearson's correlation.

3. Results

Statistical t test for independent samples indicates no significant differences between groups concerning age ($t(32) = -.166$; $p > .05$). In addition, Mann–Whitney tests show that the groups did not differ in terms of years of education ($Z = -1.803$, $p > .05$) and socio-economical status ($Z = -.036$; $p > .05$). Information about socio-demographic characteristics is presented in Table 1.

Mean distribution of FSIQ in WS is within moderate mental retardation interval (mean FSIQ $= 50.18$, $SD = 5.70$). Indeed,

Table 1 – Socio-demographic characteristics.				
	Williams Syndrome ($n = 17$)		Control group ($n = 17$)	
	M (SD)	Range	M (SD)	Range
Age	17.35 (6.74)	7–31 years	17.74 (6.69)	7–32 years
	Mdn		Mdn	
Years of education	6 years	3–12 years	9 years	3–12 years
Socio-economic status	4	1–5	4	1–5
Gender				
Male	35.3% ($n = 6$)		35.3% ($n = 6$)	
Female	64.7% ($n = 11$)		64.7% ($n = 11$)	

when FSIQ values are classified according to intellectual disability severity,[1] 76.5% ($n = 13$) show moderate intellectual disability (FSIQ between 40 and 54) and 23.6% ($n = 4$) mild intellectual disability (FSIQ between 55 and 70). When IQ distribution was related to age in WS, no significant correlation was found between age and FSIQ ($r = .172$, $p = .509$), although in WS adults group ($n = 10$), FSIQ is higher ($M = 51.70$, $SD = 4.72$, range 46–61) than children and adolescents group ($n = 7$) ($M = 48.00$, $SD = 6.63$, range 46–61).

When compared with normal development group, WS group evidences significant lower values in FSIQ ($t(32) = -14.717$, $p < .001$) and composite measures of VIQ ($t(32) = -12.249$, $p < .001$) and PIQ ($t(32) = -14.653$, $p < .001$) (see Table 2 and Fig. 1).

When composite results derived from Wechsler Intelligence Scale were analysed within WS group, a tendency was evident to score higher on VIQ ($M = 55.53$, $SD = 7.91$) than PIQ ($M = 51.65$, $SD = 5.05$), even though without reaching statistical significance ($t(16) = 2.067$, $p = 0.055$). Given the differences between WISC-III and WAIS-III, we compared VIQ and PIQ separately for children and adolescents. Thus, paired samples' t test showed no significant differences between VIQ and PIQ both in children ($n = 8$, $t(7) = 1.098$, $p > .05$) and in adults ($n = 9$, $t(8) = 1.940$, $p > .05$).

Concerning the three factorial indexes of Wechsler Intelligence Scale, participants with WS scored higher on Verbal Comprehension Index (superior score: $M = 57.88$, $SD = 9.37$) and lower in Speed Processing ($M = 55.35$, $SD = 6.81$) and Perceptual Organization Indexes ($M = 53.71$, $SD = 4.63$). When these scores were compared with normal development group, WS participants had significantly lower scores in all factorial indexes of Wechsler Intelligence Scale: Verbal Comprehension Index ($t(32) = -11.425$, $p < .001$), Perceptual Organization ($t(32) = -15.866$, $p < .001$) and Speed Processing Indexes ($t(32) = -17.828$, $p < .001$).

Finally, in all subtests of Wechsler Intelligence Scale, WS scores are globally poor and significantly inferior to the control group, with some oscillation between different subtests (Table 3). Indeed, a detailed analysis of subtest performance in WS group shows that they exhibit higher scores in Digit Span, Vocabulary and Similarities, contrasting with the lowest score on Block Design Test. This pattern of performance matches WSCP, previously defined by Mervis and collaborators.[23] Specifically, we compared levels of performance within this cognitive profile. Thus, T score on Digit Span, Vocabulary or Similarities >1st percentile (WSCP1), T score on Block Design <20st percentile. T score on Block Design < mean T score (core tests), this difference being significant [paired t tests: $t(16) = -4.607$, $p < .001$] (WSCP3) and T score on Block Design < T score on Digit Span [paired t tests: $t(16) = -4.444$, $p < .01$] (WSCP4).

Also, and consistent with these results, there is an overlap between T scores in several measures in both control and WS groups, particularly in the strong cognitive domains assessed by WSCP. However, range in scaled scores of measures, such as Coding and Block Design, is distant from scaled scores of normal controls (Table 3).

4. Discussion

Overall, this study shows that the majority of our individuals with WS (76.5%) have a FSIQ within moderate mental retardation interval. These results are consistent with other studies reporting that global intellectual functioning in WS is characterized by mild to moderate mental retardation.[4–7,15,26,31] However, there are some differences with respect to the values found in this clinical group in other studies. First, mean FSIQ values are slightly inferior to those reported in some studies (~ 55).[4,7,16] Second, FSIQ of all our subjects were ranging in mild to moderate mental retardation interval, with no subject scoring on the borderline interval. Interestingly, previous studies carried out also in Portugal and Spain

Table 2 – VIQ, PIQ and FSIQ in Williams Syndrome and control group.						
IQ	Williams Syndrome ($n = 17$)		Control group ($n = 17$)		$t(32)$	p
	M (SD)	Range	M (SD)	Range		
Verbal IQ	55.53 (7.91)	46–73	101.41 (13.27)	80–121	−12.249	<.001
Performance IQ	51.65 (5.05)	46–61	99.82 (12.58)	78–121	−14.653	<.001
Full scale IQ	50.18 (5.70)	40–61	100.47 (12.88)	77–124	−14.717	<.001
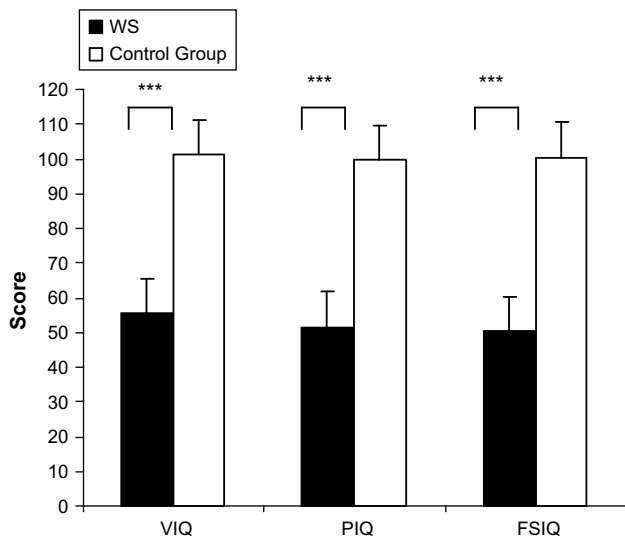
Fig. 1 – Performance in Wechsler Intelligence Scale in WS and control groups (*p < .001).**

did not find borderline IQ scores in WS participants.[13,14] This result suggests the possible existence of an underdiagnosed subcategory of good functioning WS population in Portugal and North of Spain, which are not referred to genetic counselling.

Although there is a trend for a significant difference between VIQ and PIQ, this difference disappeared when we analysed this difference according to the test used, suggesting that rather than a true difference between these measures, this effect was due to a methodological artefact, suggesting that individuals with WS display similar performance in both measures that is consistent with other studies.[6,7,15] In addition, in factorial indexes, no primacy of Verbal Comprehension Index over Speed Processing and Perceptual Organization Indexes was found. These data question the widespread idea that verbal component of intelligence is clearly superior to performance component.[16] The apparent ability in interpersonal dimensions

of language (e.g., audience hookers) may inflate our clinical impression of a spared verbal functioning[14,19] which is not confirmed by an objective evaluation of Verbal IQ. Indeed, the ability that individuals with WS have to engage people in social interactions and their relative preservation of the social-expressive component of narrative construction[2,4,14] may account for the idea of proficient language abilities. In addition, performance in tasks from PIQ subscales may be affected by the visuo-spatial and motor coordination dimensions, areas that are severely impaired in WS. In fact, some authors have suggested that IQ tests may not clearly reflect the real intellectual functioning in these individuals due to their generalized distractibility, visuo-motor coordination and difficulties in following test instructions.[27]

Comparing WS with control group, there are statistical significant differences in all dimensions of the Wechsler Intelligence Scale. These data confirm that all cognitive functions are impaired in WS; therefore, the analysis of preserved cognitive areas of performance must be obtained within the cognitive profile of WS (comparing strong and weak areas) and through comparisons with other groups with intellectual disability.[19]

A detailed analysis from Intelligence Scale subtests clearly demonstrates the typical heterogeneity of their cognitive phenotype which is consistent with the Mervis et al.[23] definition of the Williams Syndrome Cognitive Profile (WSCP). WSCP predicts that WS performance should reflect: (1) superior scores in measures of verbal abilities and impairments in visuo-constructive ability; (2) a better performance in Auditory Memory relative to Pattern Construction. Therefore, the results of this study seem to match the WSCP proposed by Mervis et al.,[23] with the finding of a higher performance in Digit Span and Similarities subtests, along with a severe impairment in performing Block Design subtest.

Contrary to what is typical with other developmental disorders with a cognitive decline as the participants age,[9,10] no significant correlation between age and FSIQ was found in our sample. These data are consistent with other studies, showing that IQ remains stable during adulthood.[16,26] However, a longitudinal study of these individuals would be needed to more accurately test this developmental pathway.

Table 3 – Wechsler Intelligence Scale subtests in WS and control group.

T scores	Williams Syndrome ($n = 17$)		Control group ($n = 17$)		t (32)	p
	M (SD)	Range	M (SD)	Range		
Picture completion	2.29 (2.34)	1–8	10.65 (2.32)	6–14	−10,461	<.001
Information	2.24 (1.75)	1–7	9.06 (2.41)	5–13	−9444	<.001
Coding	1.65 (0.93)	1–4	10.88 (2.09)	8–15	−16,654	<.001
Similarities	3.59 (2.87)	1–9	11.47 (3.47)	7–18	−7218	<.001
Picture arrangement	2.35 (1.54)	1–5	8.94 (2.44)	6–14	−9428	<.001
Arithmetic	2.76 (2.70)	1–8	10.12 (3.08)	6–15	−7396	<.001
Block design	1.29 (0.69)	1–3	9.82 (2.90)	6–14	−11,805	<.001
Vocabulary	3.06 (2.28)	1–8	9.35 (2.18)	6–14	−8237	<.001
Objects assembly	2.06 (1.56)	1–6	9.63 (2.78)	6–13	−9567	<.001
Comprehension	2.76 (2.22)	1–10	11.65 (2.76)	8–17	−10,334	<.001
Symbol[a]	2.62 (2.47)	1–9	10.44 (1.75)	7–14	−9978	<.001
Digit span[b]	4.43 (2.65)	1–10	11.06 (2.64)	8–19	−6845	<.001

a WS ($n = 13$) and control group ($n = 16$).
b WS ($n = 14$) and control group ($n = 16$).

In sum, data obtained from this study confirm the presence of intellectual disability, and evidence general deficits, both in verbal and performance components. Interestingly, in spite of the small sample size, our clinical sample is remarkably homogenous, suggesting that the range of intellectual functioning in our individuals with WS occurs within a limited interval. In addition, we confirmed the absence of an age-associated cognitive decline, which is distinct from other neurodevelopmental disorders that evidence a progressive deterioration course in intellectual functioning.

Acknowledgements

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