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Balance function in patients with Williams syndrome

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ABSTRACT

Impaired control of balance has been described in Williams syndrome (WS). The aim of this study was to investigate balance function by means of clinical and instrumental tests in order to measure postural sway in people with WS in an objective way. 23 WS patients (11 males, 12 females, mean age 17.52 ± 8.33 years) and 23 healthy subjects (11 males, 12 females, mean age 17.74 ± 8.93 years) performed static posturography with eyes open and closed, on a firm surface and on foam pads. The WS patients had higher mean length, velocity and surface values than controls under all of the test conditions, and their length and surface values were significantly higher in the eyes open test. The cognitive abilities of the WS patients were not related to their stabilometric performance. The greatest differences between the WS patients and the controls were found mainly in the older subjects. WS patients are more unstable than healthy subjects of the same age, particularly when they use visual information to maintain their balance: i.e. under conditions of normal everyday life. Possible explanations may be the ophthalmologic problems and the visuospatial difficulties attributed to a neural processing abnormality involving the dorsal stream impairment model. The balance function of WS patients is different from that of normal developing subjects, especially after adolescence when postural control is generally complete. This suggests an atypical developmental trajectory.

1. Introduction

Williams syndrome (WS) is a rare genetic multisystemic neurodevelopmental disorder that occurs in 1 in 7500 people [1]. It is caused by a hemizygous contiguous gene deletion on chromosome 7 (7q11.23 region), affecting approximately 28 genes [2]. WS is associated with a variety of medical features such as dysmorphic facies, cardiovascular disease, short stature, connective tissue abnormalities, idiopathic hypercalcemia and auditory allodynia. WS patients commonly present with a distinctive behavioural and cognitive profile including cognitive disabilities and learning difficulties, weakness in visuospatial construction and sensory modulation, relatively well preserved auditory rote memory and expressive language abilities and a strong attraction to music. Their typical personality is characterised by overfriendliness, anxiety, attention problems and heightened emotional reactions [3–8]. Moreover, visual abnormalities are rather common in WS: strabismus has been reported in 29–79% of patients [9–14] and visual acuity deficit in about 50% of patients [11].

Balance disorders, such as instability and motor coordination difficulties, have also been described in WS [7,15,16]. A significant psychomotor delay is present in all infants along with muscle tone abnormalities that vary across the life span: hypotonia has been observed especially in early childhood [17,18] while increased muscle tone has been seen in older children as well as progressive joint limitation and hyperreflexia of the lower extremities [7,15,16]. Gagliardi et al. [15] hypothesised that increased muscle tone could be part of a soft extrapyramidal pattern that becomes evident as subjects with WS mature. While WS is not typically regarded as a cerebellar syndrome, there is converging neurobiological and neurological evidence for subtle cerebellar dysfunction including impaired control of balance and abnormalities in fine motor coordination, tone and gait prevalent in early childhood and extending into adulthood [15,16,19]. Difficulties in motor activities requiring visuomotor integration, such as climbing stairs, have been explained by impaired use of visual depth information to guide movements, especially when deprived of visual feedback

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[20]; on the other hand, according to the "dorsal stream impairment model" proposed by Atkinson and Braddick [21], the impairment in a complex visuomotor task could be due to a combination of visuomotor deficit, cognitive spatial deficit and executive/attentional impairment.

Balance function is a complex multi-sensorial process relying on visual, vestibular and proprioceptive systems. Balance can be evaluated using clinical and instrumental tests; computerised static posturography is a reliable and non-invasive technique that measures body sway in an objective manner [22]. Despite several reports of balance abnormalities, no study has been conducted on balance performance in patients with WS using stabilometric platforms. The aim of the present work was to investigate the balance function in WS syndrome in a sample of 23 WS patients, children and young adults, using clinical tests and static posturography and to compare it with a control group of normal subjects.

2. Methods

2.1. Participants

23 subjects affected by WS (11 males, 12 females) aged between 6 and 35 years (mean age 17.52 years ± 8.33) participated in the study. The patients were recruited at the Eugenio Medea Scientific Institute (Bosisio Parini, Lecco, Italy) and at the Paediatric and Genetic Units of the University of Milan where they were enrolled in a multidisciplinary follow-up study. The diagnosis had been established clinically and confirmed with FISH genetic testing that showed the classical 7q11.2 microdeletion. Exclusion criteria included hearing loss (defined by a Pure Tone Average > 20 dB HL), severe visual impairment and major neurologic symptoms.

All of the WS participants or their parents (if minors or legally dependent) signed an informed consent document authorising the use of clinical data for research purposes.

The general intelligence competencies of the WS participants were assessed by age-appropriate Wechsler Intelligence Scales. The results are expressed as Full Scale IQ scores.

The control group included 23 healthy subjects (11 males and 12 females) aged between 6 and 40 years (mean age 17.74 years ± 8.93) with average cognitive and learning development; none of them presented with motor disorders and neurologic or audiological difficulties. All had normal hearing (PTA ≤ 20 dB HL); 20/23 subjects had normal visual acuity and 3/20 subjects had myopia corrected by lenses. The two groups were matched for age and gender.

For the analysis of the results, first we examined the performance of the whole sample, then we divided the sample into two age-related subgroups:

- children/young adolescents aged < 15 years. WS subjects: $n = 11$ (five males and six females), mean age: 11.18 ± 2.86 years. Control group subjects: $n = 10$ (six males and four females), mean age: 10.60 ± 2.32 years. There was no statistically significant difference (p = ns) between the two groups.
- older adolescents and adults aged ≥ 15 years: WS subjects: $n = 12$ (six males and six females), mean age: 23.33 ± 7.36 years. Control group subjects: $n = 13$ (five males and eight females), mean age: 23.23 ± 8.18 years. There was no statistically significant difference (p = ns) between the two groups.

Age, gender, height and weight in the WS group and in the control group are reported in Table 1.

2.2. Experimental set-up

A complete neurologic examination, including clinical balance assessment, was performed on 20/23 patients with WS as in Gagliardi et al. [15]. Data were clustered in pyramidal, cerebellar, extrapyramidal and general soft signs. Ophthalmic and orthoptic examinations were carried out on 21/23 WS subjects. Each participant underwent an audiological evaluation consisting of otoscopic examination, pure-tone audiometry, tympanometry and measurement of the acoustic reflex, carried out at one of two sites: the Audiology Unit of IRCCS Eugenio Medea, Bosisio Parini (Lecco) and the Audiology Unit of the University of Milan.

Static posturography was performed with the subject standing on a "SVeP 6.0" stabilometric platform (Amplifon, Milan, Italy) according to manufacturers' instructions dated September 2006. This is a stable force-plate mounted on three strain-gauge force transducers positioned at the vertices of an equilateral triangle, which is sensitive to vertical force and provides a description of body sway in terms of displacement of the patient's centre of pressure. Tests were carried out using a fixed visual target (vertical line) placed at a distance of 1.20 m at eye level. Participants with refractive disorders wore lenses during the test. The sway length (LX), sway velocity (VM) and sway area (SX) were recorded at 10 Hz for 26 s, using the SVeP software (SVeP 6.4). LX (in mm) shows the total distance covered by the centre of pressure of the subject; VM (in mm/s) is the length pro time unit; SX (mm^2) represents the surface of the confidence ellipse based on 90% of the sample positions. All subjects underwent static posturography in four specific conditions: stable foot support surface with eyes open (EO) and closed (EC), unstable foot support surface with eyes open (PAD EO) and closed (PAD EC). Unstable condition tests were performed using a monolayer rubber foam pad with a thickness of 10 cm and a specific weight of 40 g/dm^3 [23].

2.3. Statistical analysis

The data were statistically analysed using 'SPSS®' programs. Because of the small number of subjects in each group, the Mann–Whitney non-parametric test was used to compare the two groups (WS and controls). Statistical analysis was also performed between age-related subgroups: younger and older than 15 years. Exact Wilcoxon signed-ranks tests (two-tailed) were performed in order to analyse the differences between younger and older WS subjects and between younger and older controls. Pearson correlation index was calculated between IQ scores, cerebellar and extrapyramidal signs, and each posturographic parameter. A p_value < 0.05 was considered statistically significant.

3. Results

As in Gagliardi et al. [15] no major neurological sign was detected, but the majority (16/20 = 80%) of the participants affected by WS proved to be hypotonic upon neurological examination. Mild extrapyramidal signs (dystonic, involuntary, choreiform movements, facial grimaces, and rigidity) were documented in 65% (13/20) of the patients. Soft cerebellar signs were evident in 75% (15/20) of the participants. Fig. 1 reports the results of the clinical examination. No clinical sign was correlated with any stabilometric parameter.

The Full Scale IQ scores in our WS participants ranged from 30 to 80, with a mean value of 52.89 ± 13.05. No significant correlation was found between the Full Scale IQ scores and posturographic parameters (p = ns for LX, VM, SX) under each test condition.

Most of the WS subjects – 17/21 (80.9%) – showed ophthalmologic disorders: 15 (71.4%) had refractive errors corrected by lenses and 8 (38.0%) suffered from strabismus, of which one case was microstrabismus. The visual acuity of all the participants was within the normal range in both eyes when lenses were worn.

All of the WS subjects had normal hearing and middle ear function.

The static posturography results of the whole sample including both WS subjects and controls are shown in Table 2. WS subjects had higher values of mean LX, VM and SX than controls under all test conditions; no significant difference was found in tests with visual deprivation (EC and PAD EC) with the exception of SX in PAD EC; on the contrary, LX and SX were significantly higher in WS patients than in controls in test conditions with the eyes open (EO

Table 1
Age, gender, height and weight in the WS and in the control groups.

	n	Females (%)	Males (%)	Age (mean ± SD) (years)	Height (mean ± SD) (cm)	Weight (mean ± SD) (kg)
Williams < 15 years	11	54.5	45.5	11.18 ± 2.86	138.10 ± 14.02	35.13 ± 7.84
Controls < 15 years	10	40	60	10.60 ± 2.32	137.88 ± 14.36	31.13 ± 11.17
Williams ≥ 15 years	12	50	50	23.33 ± 7.36	146.20 ± 12.31	42.90 ± 12.70
Controls ≥ 15 years	13	61.5	38.5	23.23 ± 8.18	167.50 ± 10.85	59.13 ± 7.68