FLEX CEUs

Prader Willi: Therapy Considerations

Learning by observation and learning by doing in Prader-Willi syndrome

Abstract

Background: New competencies may be learned through active experience (learning by doing) or observation of others' experience (learning by observation). Observing another person performing a complex action accelerates the observer's acquisition of the same action, limiting the time-consuming process of learning by doing. Here, we compared learning by observation and learning by doing in individuals with Prader-Willi syndrome (PWS). It is hypothesized that PWS individuals could show more difficulties with learning by observation than learning by doing because of their specific difficulty in interpreting and using social information.

Methods: The performance of 24 PWS individuals was compared with that of 28 mental age (MA)- and gender-matched typically developing (TD) children in tasks of learning a visuo-motor sequence by observation or by doing. To determine whether the performance pattern exhibited by PWS participants was specific to this population or whether it was a nonspecific intellectual disability effect, we compared the PWS performances with those of a third MA- and gender-matched group of individuals with Williams syndrome (WS).

Results: PWS individuals were severely impaired in detecting a sequence by observation, were able to detect a sequence by doing, and became as efficient as TD children in reproducing an observed sequence after a task of learning by doing. The learning pattern of PWS children was reversed compared with that of WS individuals.

Conclusions: The observational learning deficit in PWS individuals may be rooted, at least partially, in their incapacity to understand and/or use social information.

Keywords: Observational learning, Learning by trial and error, Imitation, Sequential learning, Genetic disorders, Social learning

Background

Prader-Willi syndrome (PWS) is a genetic disorder with an incidence rate at birth of about 1:15,000 to 1:20,000 caused by paternal deletion within 15q11-q13 (70% to 75% of cases), maternal disomy of chromosome 15 (mUPD) (20% to 25%), or unbalanced translocation or imprinting center defect (2%) [1,2]. PWS is characterized by hyperphagia; early-onset and morbid obesity if appropriate treatments (growth hormone treatment, diet and exercise regimes) are not provided; hypogonadism; hypotonia; maladaptive behavior, such as repetitive and stereotypical behavior, mental rigidity, impulsiveness, temper outbursts, and resistance to change; and impaired social functioning [3-5]. PWS individuals are characterized by a downward shift in the distribution of IQ scores and mild to moderate intellectual disability (ID) [6]. Their cognitive profile is characterized by strengths in long-term memory, visual perception, simultaneous processing, reading skill, and visuo-spatial functions and weaknesses in attention, short-term memory, sequential processing, executive functions, action-based visual processing, auditory processing, mathematical skills, language abilities, and social cognition [7-16].

Although the behavioral phenotype of PWS individuals has been characterized with regard to maladaptive behavior and cognitive profile (for a review, see [3]), their social functioning has been only recently examined. Social

impairment exhibited by PWS individuals represents a deficit that is not merely a consequence of their maladaptive behavior, but it may reflect their specific difficulty in interpreting and using social information, such as emotional and nonverbal cues, facial emotional expressions, other's mental and feeling states, and visual information into a coherent social story [16-19]. Most reports describe PWS people as characterized by poor peer relationships, social withdrawal, and preference for solitary activities [20,21]. Furthermore, they often display aggressive behavior and a deficitary comprehension of other's thoughts or perspective [17,22].

To date, no research has analyzed whether different learning modalities facilitate or hinder the acquisition of new skills in PWS individuals. New competencies may be learned through active experience (learning by doing) or through observation of others' experience (learning by observation) [23,24]. While learning by doing involves direct experience, learning by observation involves social processing, with all the other variables (for example, motor and cognitive complexity) being equal. Observing another person performing a complex action and solving a problem accelerates the observer's acquisition of the same action, limits the time-consuming process of learning by trial and error, and reduces the practice needed to learn the skill [24,25]. Thus, it represents a powerful learning mechanism that may be based also on social processing [26-28].

The present research compared learning by observation and learning by doing in PWS individuals. It is hypothesized that PWS individuals show more difficulties with learning by observation than learning by doing because of their specific difficulty in interpreting and using social information.

The participants learned a visuo-motor sequence by performing the task after observing an actor detect the sequence of correct items by trial and error (learning by observation) or by actually detecting the correct sequence by trial and error (learning by doing) (Figure 1). The same visuo-motor task was previously used in studies of individuals with Williams syndrome (WS), dyslexia, and autistic spectrum disorders [29-31]. The task is suitable for studying the declarative and procedural components of learning. The performances of PWS individuals were compared with those of a mental age (MA)- and gender-matched group of typically developing (TD) children. To determine whether the performance pattern exhibited by PWS participants was specific to this population or whether it was a nonspecific ID effect, we compared the PWS performances with those of a third MA- and gender-matched group of WS individuals [30]. The study design that matched three experimental samples allowed us to take into account whether the learning performance of PWS individuals was better or worse than expected given their general level of intellectual functioning indexed as MA (MA-matched control group) and whether the performances were due to the cognitive profile of their specific pathology considering IQ (ID-matched control group) [10,32].

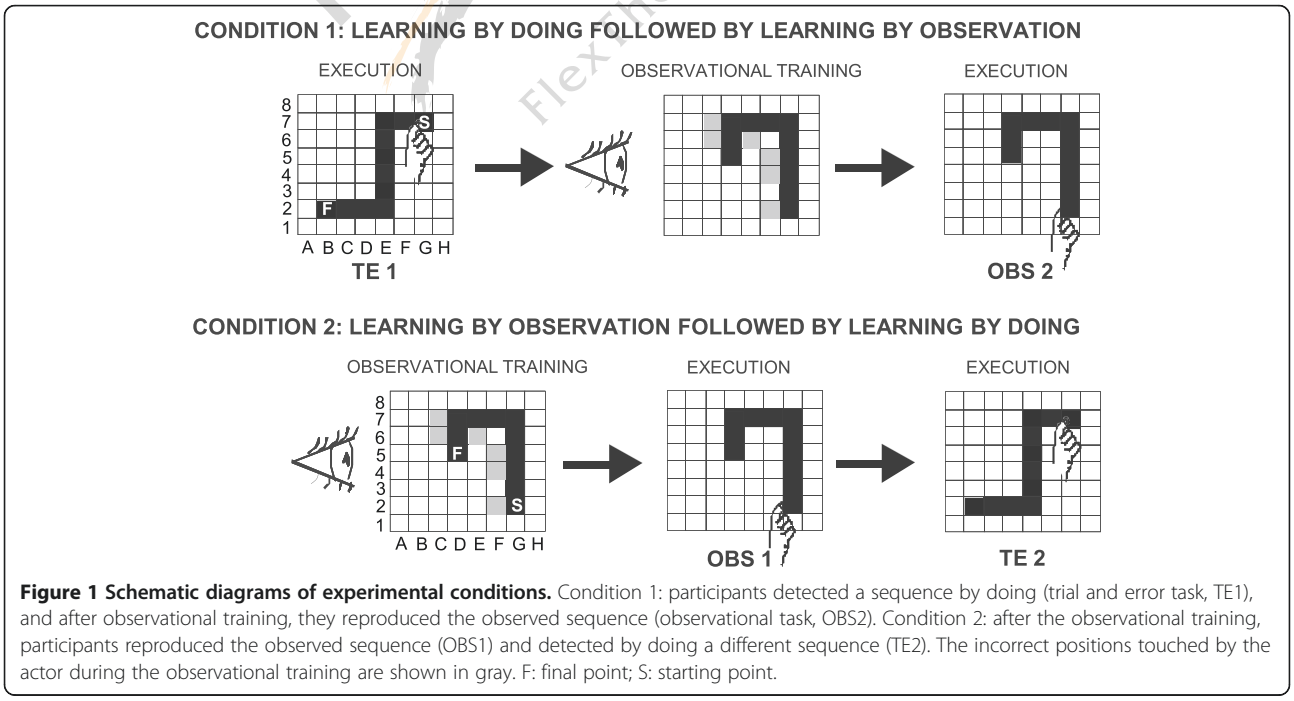

Figure 1 Schematic diagrams of experimental conditions. Condition 1: participants detected a sequence by doing (trial and error task, TE1), and after observational training, they reproduced the observed sequence (observational task, OBS2). Condition 2: after the observational training, participants reproduced the observed sequence (OBS1) and detected by doing a different sequence (TE2). The incorrect positions touched by the actor during the observational training are shown in gray. F: final point; S: starting point.

Methods

Participants

Twenty-four individuals with PWS, 24 individuals with WS (syndromic control group), and 28 TD children (control group) matching the PWS and WS groups for MA and gender were examined. Eight individuals with WS and five TD children participated in both the present study as well as our recent research [30]. The stability of data displayed by WS participants was verified as described in Additional file 1: Table S1. The present study encompassed two experimental conditions: learning by doing followed by learning by observation (Condition 1) and learning by observation followed by learning by doing (Condition 2) (Figure 1; Table 1). The participants were randomly assigned to the two experimental conditions. Chronological age (CA) and MA, as well as IQ, of all participants are compared in Table 1.

All pathological participants were part of a larger pool of individuals attending the Children's Hospital Bambino Gesù for clinical and rehabilitative follow-up. In the PWS and WS participants, clinical diagnosis was confirmed by genetic investigation (fluorescence *in situ* hybridization (FISH)), which showed paternal deletion on chromosome band 15q11-q13 in the PWS group and deletion on chromosome band 7q11.23 in the WS group. All PWS participants had been receiving growth hormone therapy for ≥3 years and were in euthyroidism. All participants lived with their own families.

While TD children were individually tested in a quiet room at their schools, all syndromic participants were tested in a quiet room at the Children's Hospital Bambino Gesù. The study was conducted according to the Declaration of Helsinki. The parents of participants gave written informed consent.

Intelligence evaluation and neuropsychological assessment

The brief version of the Leiter International Performance Scale–Revised (four out of 10 subtests: figure ground, form completion, sequential order, and repeated patterns) was used to compute brief IQ and the corresponding MA [33]. Visuo-motor integration and memory functions were assessed by visuo-motor integration (VMI) [34], visuo-spatial short-term memory (VSS), and visuo-object short-term memory (VOS) tests [35]. Description of tests and statistical comparisons among groups are reported in Table 2 and Additional file 2: Table S2.

Experimental procedure

Each participant sat in front of a computer touch screen (distance 60 cm). In both conditions, the experimenter acting as the actor (FF) sat near the participant. An 8 × 8 black matrix appeared on the touch screen. The participant was asked to find a hidden sequence of correct squares prepared in advance by the experimenters. The sequence was composed of ten adjacent spatial positions in the matrix, which formed a snake-like pattern (Figure 1).

To explain the task to each participant, the experimenter used the same Italian verbal instructions because all participants were native Italian speakers. Below is the translation of the verbal instructions provided to all participants: 'You have to find a snake formed by ten squares. When you touch a correct square belonging to snake body it will be turned gray and you will hear a sound; conversely, if you touch a wrong square not belonging to the snake, it will be turned red. In this case, you have to find a new gray square. You have to re-start each time you find a new correct square. After finding the whole snake, you have to re-touch it three times without making lighted red squares.' The participants started touching a gray square, which was the first element of the sequence representing the snake body and was always lit up. In the search for the second correct square, the participants had to touch one of the four squares bordering the gray square by moving in the matrix vertically or horizontally, but never diagonally. Each touched square (correct or wrong) was lit up for 500 ms and then lighted off again; thus, no trace of the touched sequence remained on the screen.

In learning the sequence by trial and error (learning by doing), the participants tried to find the correct sequence immediately after the verbal instructions. Conversely, in learning the sequence by observation, after the verbal instructions the participants observed the actor while she (FF) detected a ten-item sequence by trial and error (observational training). The actor performed the task by always making the same errors in the same positions, so that all participants observed the same pattern of correct and wrong touches. No more than 2 min after the

Table 1 Statistical comparisons (one-way ANOVA) of CA, MA, and IQ between PWS, WS, and TD groups

Group	CA Mean (±SEM)	$F_{(fd)}$ P η_P^2	MA Mean (±SEM)	$F_{(fd)}$ P η_P^2	IQ Mean (±SEM)	$F_{(fd)}$ P η_P^2
PWS1 (Condition 1)	21.08 (±2.06)	$F_{1, 22} = 1.16$, $P = 0.29$, $\eta_P^2 = 0.05$	6.02 (±0.01)	$F_{1, 22} = 0.70$, $P = 0.41$, $\eta_P^2 = 0.03$	51.8 (±2.6)	$F_{1, 22} = 0.07$, $P = 0.79$, $\eta_P^2 = 0.003$
PWS2 (Condition 2)	18.05 (±1.08)		6.05 (±0.03)		52.7 (±2.9)	
WS1 (Condition 1)	20.05 (±2.04)	$F_{1, 22} = 0.59$, $P = 0.45$, $\eta_P^2 = 0.03$	6.04 (±0.02)	$F_{1, 22} = 0.07$, $P = 0.78$, $\eta_P^2 = 0.003$	54.2 (±2.7)	$F_{1, 22} = 0.01$, $P = 0.90$, $\eta_P^2 = 0.0006$
WS2 (Condition 2)	17.06 (±2.02)		6.05 (±0.03)		53.8 (±2.2)	
TD1 (Condition 1)	6.06 (±0.02)	$F_{1, 26} = 0.03$, $P = 0.85$, $\eta_P^2 = 0.001$	6.06 (±0.03)	$F_{1, 26} = 0.69$, $P = 0.41$, $\eta_P^2 = 0.03$	103 (±3.1)	$F_{1, 26} = 2.27$, $P = 0.14$, $\eta_P^2 = 0.08$
TD2 (Condition 2)	6.07 (±0.02)		6.04 (±0.03)		109.1 (±2.7)	

Table 2 Statistical comparisons (one-way ANOVA) of performances of PWS, WS, and TD participants

Cognitive domain	PWS Mean (±SEM)	WS Mean (±SEM)	TD Mean (±SEM)	Group effect $F_{(fd)}$ P η_P^2	*Post hoc* Newman-Keuls's test *P*; Cohen's *d*; *r*
VMI	13.08 (±0.54)	12.79 (±0.52)	15.14 (±0.28)	$F_{2,\ 73} = 8.51$	PWS vs. WS
				$P = 0.0005$	$P = 0.65$; $d = 0.11$; $r = 0.05$
				$\eta_P^2 = 0.19$	PWS vs. TD
					$P = 0.002$; $d = -0.96$; $r = -0.43$
					WS vs. TD
					$P = 0.001$; $d = -1.12$; $r = -0.49$
VSS	3.35 (±0.14)	2.63 (±0.19)	3.43 (±0.16)	$F_{2,\ 73} = 6.50$	PWS vs. WS
				$P = 0.003$	$P = 0.004$; $d = 0.84$; $r = 0.39$
				$\eta_P^2 = 0.15$	PWS vs. TD
					$P = 0.75$; $d = -0.09$; $r = -0.05$
					WS vs. TD
					$P = 0.004$; $d = -0.87$; $r = -0.40$
VOS	2.79 (±0.15)	2.71 (±0.13)	2.89 (±0.13)	$F_{2,\ 73} = 0.48$	
				$P = 0.62$	
				$\eta_P^2 = 0.013$	

VMI, visuo-motor integration; VSS, visuo-spatial short-term memory; VOS, visuo-object short-term memory.

end of the observational training, the participants were required to reproduce the correct sequence (the snake).

Parameters

Regardless of whether learning took place by observation or by doing, the two tasks involved three phases: the detection phase (DP) that ended once the participants found the tenth correct position, the exercise phase (EP) in which they had to repeat the ten-item sequence until their performance was error-free, and the automatization phase (AP) that ended when the correct sequence was repeated three consecutive times without errors.

The parameters measured were as follows: DP errors, calculated as the number of incorrect items touched in detecting the ten correct positions; EP repetitions, calculated as the number of replications needed to reach the error-free performance; and AP times (in ms), calculated as the time spent carrying out each of the three repetitions of the sequence. Considering DP and EP together, we calculated perseverations, consecutive errors touching the same square or a fixed sequence of squares; sequence errors, touching a correct square at the wrong moment (for example, touching E7 before F7); side-by-side errors, touching the squares bordering the correct sequence (for example, E8); illogical errors, touching any other square (for example, B5); and, exclusively in the observational learning task, imitative errors, touching the squares deliberately wrongly touched by the actor during the observational training (for example, F4) (Figure 1).

The error analysis allowed a multi-faceted characterization of the performance. Specifically, sequence and side-by-side errors allowed analysis of mnesic, planning, and inhibitory abilities, and cognitive flexibility. Illogical errors permitted analysis of adherence to the experimental setting and understanding the task instructions. Finally, imitative errors provided information on the tendency to adhere to the behavior of the social model (actor) and hyperimitate it, because the observational learning did not merely involve copying an action but required that the observer transformed the observation into an action as similar as possible to the model in terms of the goal (detecting the snake) to be reached. The hyperimitative tendency is faithfully copying both necessary and unnecessary actions made by the actor. Besides a reduced understanding of the rules of the task, hyperimitation may reflect a social process linked to the individual's motivation to affiliate with the demonstrator or to closely conform to perceived norms [36,37]. Therefore, the analysis of the imitative errors is important to facet the features of the learning by observation.

Condition 1: learning by doing followed by learning by observation

Twelve PWS, 12 WS, and 14 TD participants (Table 1) detected a sequence by doing (trial and error task, TE1), and after 10 min from task end, they observed the experimenter detect a different sequence (observational training). After 2 min, participants were required to reproduce the observed sequence (observational task, OBS2). There was no fixed time limit for executing the task.

Although the two sequences to be used as TE and OBS sequences had two different forms, their degree of

difficulty did not differ because both sequences had the same number of squares (10) and corners (2). To confirm this assumption, a pilot study was conducted. Six TD children [four males] of MA 6.04 ± 0.2 years detected the two different sequences by doing; the presentation order was randomized among participants. DP errors made in detecting TE ($\bar{x}$ = 24.83 ± 2.57) and OBS ($\bar{x}$ = 20.83 ± 2.19) sequences, evaluated using Wilcoxon's test, were not significantly different ($Z = 1.21$, $P = 0.22$).

Condition 2: learning by observation followed by learning by doing

Twelve PWS, 12 WS, and 14 TD participants (Table 1) observed the experimenter detect a sequence (OBS1) and then reproduced it. After 10 min from task end, they detected a different sequence by doing (TE2). The difference between the two conditions was that participants reproduced a sequence learned by observation after (Condition 1) or before (Condition 2) the detection of a different sequence by doing. This protocol encompassing the use of both tasks (OBS and TE) in each condition allowed analysis of the performances of the same participants in the two types of learning. To exclude any practice effect, inevitably present in the second tasks and potentially affecting performances, Conditions 1 and 2 (with the only change being the order of presentation) were needed.

No significant differences in CA, MA, and IQ (always $P > 0.1$) among participants performing Conditions 1 and 2 were found (Table 1).

Cognitive mapping abilities

In all participants, we evaluated the cognitive map, which was the spatial mental representation in which information about the relative locations of the squares was coded to connect them in the global sequence [38,39]. To this aim, at the end of each task (OBS or TE), every participant drew the arrangement of the just-reproduced sequence on an 8 × 8 matrix sketched on a paper sheet, in which only the starting point was indicated (Additional file 3). Each participant drew two sequences, one learned by observation and the other one by doing. We evaluated the positions of every square and considered error any marked square outside of the just-reproduced sequence. Three categories of errors were considered: no error, one error, and more than one error.

Statistical analyses

The data were first tested for normality (Shapiro-Wilk's test) and homoscedasticity (Levene's test) and then compared by using two-, three-, or four-way analyses of variance (ANOVAs) followed by *post hoc* multiple comparisons by using Newman-Keuls's test. The two-way ANOVAs were performed by applying the mixed model for independent variables (PWS, WS, and TD groups) and repeated measures (type of error: illogical, sequence, side-by-side, and imitative). Three-way ANOVAs (group × condition × task; group (PWS, WS, TD); condition (1, 2); task (OBS, TE)) were performed on DP errors, EP repetitions, and perseverations. A four-way ANOVA was performed on AP times by applying the mixed model for independent variables (group (PWS, WS, TD); condition (1, 2); task (OBS, TE)) and repeated measures (times (1, 2, 3) spent carrying out each of the three repetitions of the sequence). Error categories of mapping abilities were analyzed by the χ^2 test. Data of the pilot study were analyzed by using nonparametric analysis (Wilcoxon's test). Analyses were performed by Statistica 8.0, and the significance level was established at $P < 0.05$. Since in the present study a number of analyses was run, controlling for the alpha inflation was needed. We controlled the proportion of type I errors among all rejected null hypotheses by setting the false discovery rate (FDR) to 0.05. The FDR was estimated through the procedure described in [40]. In our results, the 0.05 level of significance corresponded to an FDR < 0.05. The complete statistical analyses are reported as Additional file 4: Table S4 and Additional file 5: Table S5.

Results

Learning tasks

In TE1, unlike WS participants, PWS participants did not differ from TD children in DP errors they performed in detecting the sequence by doing (Figure 2A). Conversely, in comparison with TD and WS participants, PWS participants performed a number of DP errors significantly higher in OBS1 but not significantly different in OBS2 and TE2 tasks (Figure 2A), as revealed by *post hoc* comparisons on the second-order interaction of the three-way ANOVA (group × condition × task) ($F_{(2,\ 70)} = 5.13$, $P = 0.0083$, $\eta_P^2 = 0.13$).

As for EP repetitions, while WS participants needed a significantly higher number in comparison to TD participants, PWS and TD participants did not differ as revealed by *post hoc* comparisons made on the group effect ($F_{(2,\ 70)} = 3.36$, $P = 0.040$, $\eta_P^2 = 0.09$) of the three-way ANOVA (group × condition × task) (Figure 2B). Even the analysis of perseverations revealed no significant difference among PWS and TD participants. Conversely, in TE1, WS individuals performed a number of perseverations significantly higher than PWS and TD participants, as revealed by *post hoc* comparisons on the second-order interaction ($F_{(2,\ 70)} = 3.18$, $P = 0.048$, $\eta_P^2 = 0.08$) of the three-way ANOVA (group × condition × task) (Figure 2C).

A similar pattern was found in the analysis of the three AP times. PWS participants exhibited AP times significantly lower than WS individuals, but not significantly different from those of TD children, as revealed by *post hoc* comparisons on the group effect ($F_{(2,\ 70)} = 8.26$,

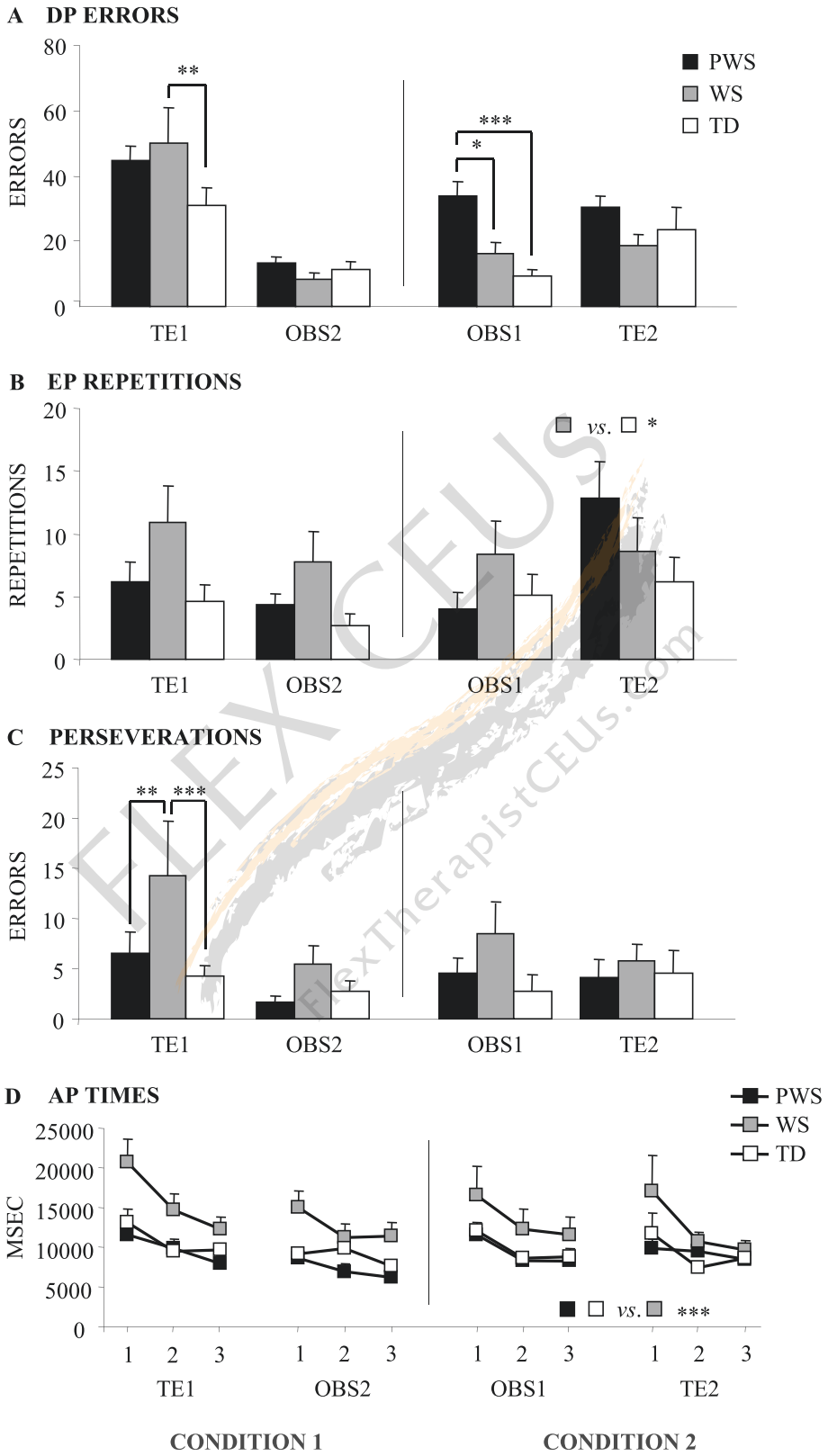

Figure 2 Performances of PWS, WS, and TD participants. (A) DP errors. **(B)** EP repetitions. **(C)** Perseverations. **(D)** AP times. Data are expressed as mean ± SEM. The asterisks indicate the significance level of *post hoc* comparisons among groups (*$P < 0.05$; ** $P < 0.01$; *** $P < 0.005$). DP: detection phase; EP: exercise phase; AP: automatization phase.

$P = 0.0006$, $\eta^2_P = 0.19$) of the four-way ANOVA (group × condition × task × time) (Figure 2D). All participants exhibited significantly reduced times as the task proceeded ($F_{(2,\ 140)} = 33.67$, $P < 0.000001$, $\eta^2_P = 0.32$), indicating a progressive automatization of the task.

Analysis of error

In OBS1, PWS individuals exhibited a number of sequence errors higher than TD children and interestingly higher than WS participants, as revealed by *post hoc* comparisons made on the significant interaction ($F_{(6,\ 105)} = 2.93$, $P = 0.011$, $\eta^2_P = 0.14$) of the two-way ANOVA (group × type of error). The PWS individuals exhibited also a number of side-by-side errors higher than TD children. PWS, WS, and TD participants did not differ in the number of illogical and imitative errors (Figures 3 and 4). The analysis of error in the remaining TE1, OBS2, and TE2 tasks revealed no significant difference among the groups, even if significant differences among errors were found (always $P < 0.000001$) (Figures 3 and 4). Also interactions were not significant.

Cognitive mapping abilities

No significant difference among groups and among error categories was found in any sequence (always $P > 0.3$), a clear index of similar cognitive mapping abilities in all groups.

Discussion

The current study aimed at analyzing learning by observation and learning by doing in PWS in comparison with WS and TD individuals. With the exception of the imitative competencies, both visuo-motor learning tasks required attentive and mnesic functions, sequencing abilities, planning, response inhibition, cognitive flexibility, good knowledge and anticipatory expectation of effects related to actions, goal-directed actions, and motor imagery allowing recombination of novel actions with novel effects [29-31,41]. The main result of the present study showed a specific PWS deficit in learning by observation. The observational training did not help PWS individuals to detect and encode information, such as rules of the task, correct moves, and goals they had to reach. PWS individuals were impaired in reproducing the previously observed visuo-motor sequence when the observational task was proposed at first (OBS1), while they were as efficient as the TD children in detecting a sequence by trial and error (TE1 and TE2) and in reproducing the previously observed sequence when proposed as a second task (OBS2). The learning pattern of PWS was the reverse of that of WS individuals who were severely impaired in detecting the visuo-motor sequence in TE1 and as efficient as TD children in OBS1.

The deficit in learning by observation found in PWS individuals may be related to the impairment in social functioning described in this population [17]. Studies on

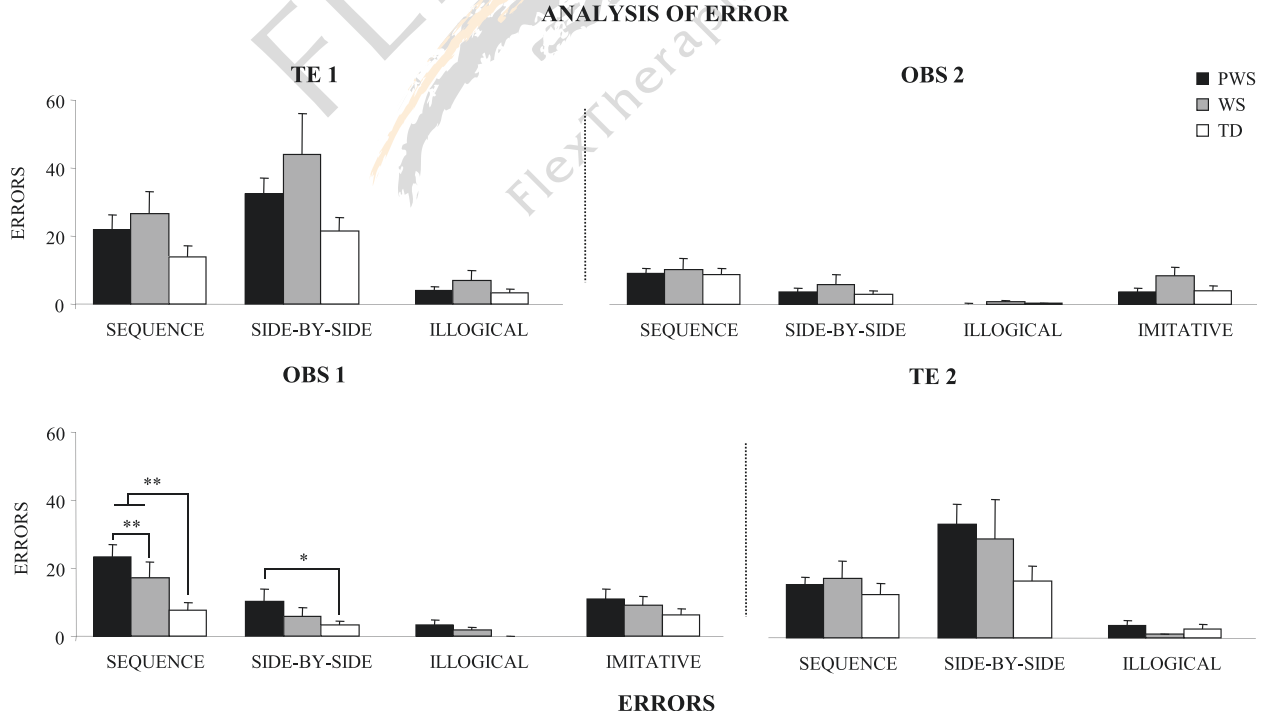

Figure 3 Errors exhibited by PWS, WS, and TD participants in the two experimental conditions. Data are expressed as mean ± SEM. The asterisks indicate the significance level of *post hoc* comparisons among groups (*$P < 0.05$; **$P < 0.01$).

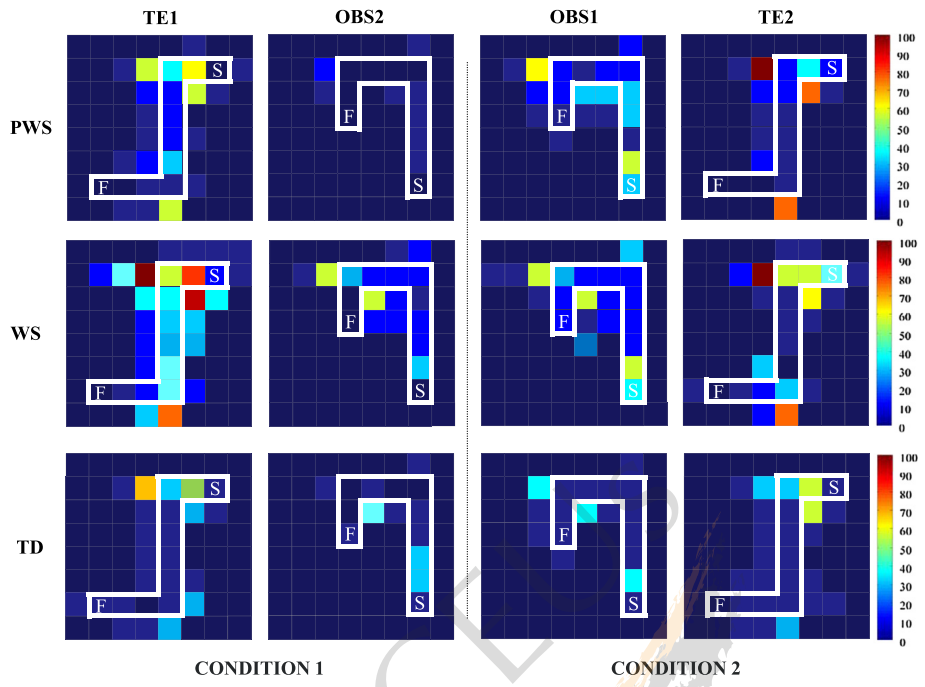

Figure 4 Incorrect items touched on the screen by PWS, WS, and TD participants in performing the tasks. On the right, the chromatic scale indicates the sum of incorrectly touched items (brown and blue denote maximal and minimal values, respectively). F: final point; S: starting point.

the social deficits present in PWS have focused on either high frequencies of stubbornness, disobedience, and obsessive/compulsive and ritualistic behaviors or solitary behaviors, social withdrawal, and poor peer relations [42-44]. Even the frequent temper outbursts of PWS individuals are attributed to their impaired capacity to understand the motivations of others in the social milieu [17]. The poor performance of PWS individuals in OBS1 suggests a specific incapacity to use the information provided by the actor. PWS individuals display difficulty in recognizing and interpreting social cues and situations on the Social Attribution Task that measures the specific abilities necessary for interpreting social information [17]. It has been suggested that in PWS individuals the few attributions of feeling in social relationships indicate their deficit in empathy and 'theory of mind.' Such a deficit may determine impairment in interpersonal processes that are crucial for developing social abilities and understanding another's thoughts and perspectives [12,45]. In a functional neuroimaging study, the typical difficulties in interacting with peers and understanding social environment displayed by PWS individuals are related to the perfusion abnormalities of the anterior cingulum and the cingulate gyrus found in these individuals [46]. Conclusively, the impaired PWS performance in OBS1 can be at least partially attributed to their difficulties in processing social information. The specular learning pattern of WS individuals (impaired TE1 and efficient OBS1) was coherent with their spared social abilities [47]. The PWS good performances in OBS2 do not contradict such an interpretation, because any second task (OBS2 and TE2) allowed overcoming the specific deficits of the clinical populations, by taking advantage of the previous experience (practice effect).

Once detected, the visuo-motor sequence had to be repeated until the error-free performance (exercise phase). The exercise phase mainly required working memory, memory load to form and maintain the trace of the correct sequence, long-term memory, and attentional demands to monitor its correct execution. Therefore, the efficient EP performance of PWS but not WS participants indicates a sparing of these abilities. Such a result complements the indication that the visuo-spatial domain is a strength point of PWS individuals [9,48,49]. Actually, the already-described PWS competence in solving spatial tasks, as for example jigsaw puzzles [50], may represent an advantage in performing the exercise phases. Also, the competent cognitive mapping abilities we found in PWS individuals point to this direction. The specular findings obtained by PWS and WS participants in EPs are related to the respective cognitive profiles. Indeed, the visuo-spatial domain is a strength point in PWS and conversely a strong weakness in WS. The WS deficits in spatial working and long-term memory [10,51-55] heavily impaired performances in all EPs. Finally, the PWS performances harmonize with the good capacity of spatial learning and localizatory memory shown by an animal model deficient of Necdin, a candidate gene in PWS etiology [56].

As for the kind of errors, all participants made an analogously low number of illogical errors, indicating that they all similarly managed the task fundamentals. Despite the specific deficit in observational learning of PWS participants, no difference in imitative errors was found among the groups. This result indicates that the imitative PWS deficit was not accompanied by a tendency to hyperimitate. The hyperimitation may be considered a tendency to affiliate or establish, maintain, and enhance relationships with the other. It may be linked to an ingratiating behavior that enhances the conformity with others [57]. Consistently, more empathic individuals and people scoring high in measures of social motivation tend to imitate [58,59]. Interestingly, PWS individuals are often hostile, with social withdrawal, put less emphasis on managing their social image, and exhibit scarce social motivation. Thus, the reduced number of imitative errors performed by PWS individuals is consistent with the social interpretation of their deficits in learning by observation. Given that people learn a lot through social interactions, the role of social motivation in the observational learning and whether a reduced social motivation may lead to impaired learning are interesting issues requiring future studies aimed to address which ways may boost learning.

In OBS1, PWS participants in comparison with TD children made more sequence and side-by-side errors when a change of direction was required. Errors in stopping the easier 'keep-straight' response and performing the more demanding 'turn-left' response resulted in the PWS participants' difficulty suppressing a previously correct but then inappropriate response. Not by chance, correctly responding requires executive control processes based on frontal function, as response inhibition, cognitive flexibility, and attentional shifting [60,61], which are already indicated to be impaired in PWS [11,62-65]. Only a few studies have investigated brain abnormalities in PWS individuals; however, it is suggested that their executive dysfunction may be associated with fronto-parietal abnormalities [65-67]. The current findings can be nicely related to those obtained in an animal PWS model with a defect in the imprinting center, in which impaired abilities related to frontal abnormalities have been described in a five-choice serial reaction time task [68,69].

In the automatization phases, while WS participants displayed slowed down automatization times, PWS and TD participants showed similar times that progressively declined as the task was repeated. Specifically, the automatization phase required automatization of sequential visuo-motor productions to increase the efficiency and speed of the response and to achieve the highest levels of performance [70]. Automatizing skills are mainly linked to the functions of subcortical structures, such as the cerebellum and basal ganglia, and to their bidirectional interconnections with cortical structures [71-73]. Therefore, the efficient automatization in PWS indicates the preserved functionality of these brain networks. Similarly, the impaired WS automatization is consistent with brain abnormalities characterized by remarkable hypoplasia of the basal ganglia and the disproportionate enlargement of the cerebellum [74-77].

The performances of PWS individuals improved dramatically in OBS2, indicating the beneficial practice effect on the ability to learn by observation. Notably, the production of actions has a strong impact on action memory, so producing actions helps remember them [78]. Thus, actively produced actions influence the accessibility of memories by enhancing both the content and strength of the memory representation [79]. In this study, others' actions appear to be linked to self-performed actions, as if agentive experience were functioning as a catalyst for action observation [80,81].

It should be emphasized that PWS individuals have language difficulties [16] that could impair their comprehension of verbal task instructions. However, the efficient performances of PWS individuals in the TE1 task (explained by means of exactly the same verbal instructions) indicated that their poor performances in OBS1 were not caused by a failure to understand the verbal instructions. If that were the case, both first tasks (OBS1 and TE1) would have been compromised.

Finally, a critical point in interpreting our results rests on our choice to adopt a between-group design, which meant that the conclusions were based on the performance of two different groups of PWS individuals. Although this design has some limitations in respect to the within-group design, we retained that a between-group design was adapted to address the differences between learning modalities. In fact, submitting people to various visuo-motor learning tasks inevitably implies a practice effect (learning effect), being difficult to propose them on different occasions, to render them different enough not to expect a change resulting from repeated testing, and to present them fully counterbalanced.

The present results could have important implications for developing interventions aimed at improving learning. In school, teaching is generally based on first showing how a task should be executed and then allowing for actual performance. The present data indicate that a useful way to improve learning in PWS individuals could be to use the 'trick' of first allowing them to actually perform a task and then eventually showing them how to refine the task that they have just experienced.

Conclusions

The present study compared two learning mechanisms, learning by observation involving social processing and learning by doing involving direct experience, with all the other variables (for example, motor and cognitive

complexity) being equal. A specific PWS deficit in learning by observation was found. Specifically, in comparison to WS and TD groups, PWS individuals were impaired in reproducing the previously observed visuo-motor sequence when the observational task was proposed first (OBS1), while they were as efficient as the TD children in detecting a sequence by trial and error (TE1 and TE2) and in reproducing the previously observed sequence when proposed as a second task (OBS2). We propose that the observational learning deficit in PWS individuals may be rooted, at least partially, in their incapacity to understand and/or use social information. As emphasized by Dimitropoulos et al. [16], there is increasing acknowledgement of social difficulties of PWS individuals above and beyond what is thought to be experienced by a person with a similar level of intellectual impairment. The characterization of their behavioral and cognitive phenotype allows for more targeted interventions aimed at stimulating and improving learning performances.

Weight control and behavior rehabilitation in a patient suffering from Prader Willi syndrome

Abstract

Background: This study reports a case of Prader Willi syndrome (PWS), a genomic imprinting disease related to chromosome regions 15q11.2–q13 15, which includes hypothalamic dysfunction leading to hyperphagia, obesity, shortness, sleep abnormalities. Our case is extremely severe, in comparison to other PWS cases described in literature, due to the association with severe emotional and psychiatric symptoms: oppositional behaviour, rigidity of thought, skin picking and pathological hoarding.

Case presentation: We described the case of a Caucasian male patient suffering from PWS, treated in outpatient care by local Mental Health Centre and supported by Social Service, who was admitted to a residential rehabilitative facility. After a 2-year follow-up, the patient showed a global improvement in symptoms and functioning, as registered by the rating scales administered. At the end of observation period, we also reported an important improvement in weight control, reducing the risk of obesity and related diseases, therefore improving the prognosis of life.

Conclusion: This case highlights the need for long-term, individualized and multi-professional treatment in patients suffering from a complex genetic syndrome with both organic and psychological alterations, for which medical care setting and pharmacological treatments are not sufficient. Clinical observation of this case leads us to compare PWS to drug addiction and indirectly endorse the neurophysiological hypothesis that food and drugs stimulate the same brain circuits in the limbic system.

Keywords: Genomic imprinting, Hypothalamic dysfunction, Hyperphagia and obesity, Aggressive behaviour, Long-term individualized rehabilitation

Background

Genetics and diagnosis

Prader-Willi syndrome (PWS), described for the first time in 1956 by the Swiss doctors from which it takes its name, presents a prevalence ranging from 1:10,000 to 1:30,000. It is present in both males and females of all races and is rarely inherited (only one person in a family is usually affected by this syndrome) [1].

PWS, the first human disorder to be recognized as related to genomic imprinting, is caused by the failure of expression of paternal genes presented in the region of chromosome 15q11.2–q13 15 [2, 3]. The main molecular mechanisms responsible for PWS are [4]:

Paternal microdeletion (75–80 % of cases); maternal disomy (UPD) (20–25 % of cases); imprinting defect (ID), (1–3 % of cases); other defects, such as balanced and unbalanced translocations, which with ID are responsible for most cases of familial inherited PWS.

A set of clinical criteria was proposed by Gunay-Aygun and collaborators [5] in order to identify the subjects which required an appropriate genetic test to diagnose PWS: poor muscle tone, reduced ability to suck milk and, if male, cryptorchidism in early childhood and delay in neurological developmental, short stature,

psychomotor retardation, obsessive behaviour, compulsive ingestion of food with obesity in middle childhood and adolescence.

PWS diagnosis requires the execution of a test called DNA methylation (specific multiplex ligation-dependent probe amplification analysis, abbreviated MS-MLPA).

Endocrinological, cognitive and behavioural alterations

Most endocrine disorders in PSW are secondary to hypothalamic dysfunction [6], which is responsible for the deficiency of growth hormone, thyroid stimulating hormone, adrenal-corticoid hormones and hypogonadism [4, 7]. The reduced secretion of gonadotropins and growth hormone condition neonatal hypotonia, short stature, puberty failure, as well as all the behavioural manifestations that are associated with this syndrome. Central hypothyroidism, with a normal value of thyroid stimulating hormone and low levels of free thyroxine, has been documented in approximately 25 % of individuals with PWS [1]. Other key symptoms, such as hyperphagia and altered control of appetite [8], alteration of sleep-wake cycle [6], dysfunction of body temperature regulation [9] and increased pain threshold [10] would be secondary to alterations in hypothalamic function [8]. Obesity in PWS is mainly central (abdomen, buttocks and thighs) in both sexes, with a reduced amount of visceral fat compared to other patients with the same degree of overweight [11]. Several studies have shown that ghrelin levels are significantly elevated before and after meals in hyperphagic individuals with PWS, especially in older children and in adults. In children with PWS has been found hyperghrelinemy [12], but this result has not been replicated in other studies [13, 14]. Some authors have examined the neural circuit that mediates appetite and eating behaviour (orbitofrontal cortex and hypothalamus) and have shown, through functional magnetic resonance imaging, that this circuit in PWS is abnormally activated during the intake of high-caloric food [15, 16]. Reduced sleep latency rapid eye movement (REM) with altered architecture of the different stages of sleep, oxygen desaturation and obstructive apnea have been reported in PWS [17].

A literature review of cognitive abilities among 575 individuals affected by PWS showed that only 5 % of these patients had a normal IQ [4]. 70–90 % of patients with PWS present behavioural disorders since childhood, characterized by impaired impulse control with bursts of anger, manipulative attitudes [4], and compulsions, in particular pathological hoarding (especially food) and skin picking [18, 19]. Some authors have observed that many of these behavioural alterations are also present in autism spectrum disorders and that both the disorders may be associated with genetic alterations of chromosome 15 [20]. Forster and Gourash [21] have identified five domains related to behavioural alterations observed in patients with PWS: hyperphagia and related behaviour, hostility, rigidity of thought, skin picking and pathological hoarding, feelings of insecurity with increased anxiety. In a Japanese study, the authors have highlighted that patients with PWS often present anxiety disorder, obsessive compulsive disorder and mood instability in comorbidity [22].

Complications are almost all related to the underlying endocrine alterations: osteoporosis with fractures, secondary hypogonadism disorders, sleep apnea, cardiovascular disease, diabetes mellitus type 2 and all complications related to the obesity that develops in almost all cases. Other complications are related to the frequent binges that can result in death due to self-suffocation, rupture of stomach and, in the case of ingestion of inedible substances, poisoning. The behavioural alterations can further complicate the course of psychological development and lead to a serious socio-environmental maladjustment [23].

The only drug therapy indicated for this syndrome is growth hormone, which was approved in 2000 by the Food and Drug Administration (FDA) for the treatment of PWS in childhood [4]. This pharmacological treatment significantly reduces the initial muscular hypotonia and the subsequent risk for the development of obesity, partially normalizes physical and psychological development and improves cognitive function. The prescription of this drug in adulthood is still debated due to the possible aggravation of diabetes and sleep apnea and the increased risk for edema and cancers [7, 11]. Many authors have identified multidisciplinary rehabilitative programs as indispensable tools to treat these patients [21, 24]. To support families and caregivers of these patients, many voluntary associations have been organized. In Italy, on 12 July 1991, sixteen families living in Lombardy founded the first association for people with Prader Willi (www.praderwilli.it) and, subsequently, other associations were founded [4].

Purpose

We describe the case of a male Patient suffering from PWS, treated in outpatient care by Mental Health Centre (MHC) and supported by Social Service since childhood, who was admitted to a residential rehabilitative facility (RRF), in April 2012. This RRF is dedicated to people with severe and very severe mental disabilities. After collecting anamnestic information of the Patient from the medical records of out- and inpatient psychiatric services and from the reports of parents and social assistants respectively, we analysed the rehabilitative program developed for the Patient in the RRF as reported in the documentation and the clinical chart of this institute. In

order to assess the multi-professional clinical outcome of 24-month rehabilitative program at the RRF, from April 2012 to 2014, we evaluated, at the end of the observation period, the number of psychiatric admissions, hematologic tests and body mass index (BMI), behavioural alterations and functioning levels by administering symptom and functioning rating scales: the Italian scale, so called "VADO": Valutazione di Abilità, Definizione di Obiettivi (evaluation of ability, definition of objectives) [25], Personal and Social Performance Scale (PSP) [26]. Finally, we report the current state of the Patient, updated in June 2015, in order to better detail the outcome of his rehabilitation program.

Case presentation

Childhood

At the age of two, the Patient was abandoned by his parents as were his brother and sister. Successively, he and his siblings were adopted by Italian parents. In the new family, our Patient lived in a detached country house with four of his adoptive brothers and two young children, sons of two adoptive brothers, presenting good relationship with all components. Shortly, in early childhood, he presented severe hyperphagia and compulsive search for food and inedible substances, developing a sort of Pica. His adoptive mother referred that he was so attracted by substances with a good smell to eat scented soaps and drink bubble baths. Also, disgusting things such as rabbit faeces or rotten rubbish were stolen and eaten by him. When he was 3 years old, he was short but already weighed 33 kg. In the meantime, he progressively developed aggressive behaviour, especially in case of prohibitions or restriction of food. At age 4, he was diagnosed with PWS by the methylation test in chromosomal region 15q11–13, which revealed the presence of a single methylated band, whose molecular evidence has been associated with the most common PWS phenotype. From that point onwards, his family implemented new restrictive rules, such as to lock the pantry or to lock him in his room during the night, in order to prevent the patient gaining weight or swallowing something inedible. Moreover, the patient's family did not buy caloric food or scented substances and put in place many distracting activities for the Patient (watching movies, completing puzzles, etc.). His mother reported that, on more than one occasion, in order to prevent poisoning, the family consulted Emergency because the Patient had ingested leaves or other vegetable products with unknown effects. From kindergarten, his attendance at school was very problematic, despite the support of teachers dedicated to him, due to many behavioural alterations, learning difficulties, inability to maintain attention, aggressiveness, intolerance to frustration, lack of socialization skills and continuous search for food. He completed middle school, but, due to his problems, was rejected by more than one high school. Finally, he enrolled in a vocational school, where he attended only the first year, which he had to repeat, before dropping out. Despite his school failure, the Patient was able to cultivate some interests such as reading, drawing and composition of puzzles. In particular, he showed great skill in performing puzzles composed of many pieces. In addition, he was really interested in horror movies and comics, which could sometimes distract him from the compulsive search for food. When he was 17 years old, the Patient ran away from home, after being discovered by his parents in the act of eating a rotten cake collected from the garbage. Readily found by the Police, he claimed not to want to return to his family, complaining about abuses suffered in his family home ("My parents lock me in my room"). Therefore, the local Social Service for Minors, promptly activated, provided for the temporary placement of the Patient in a community. In the meantime, the Patient was admitted to the psychiatric day hospital of an accredited private hospital dedicated to adolescent psychiatric patients, in order to evaluate his psychological profile (interpersonal skills, reaction to stress and tolerance for frustration) and assess, in the meantime, the ability of the family to adequately support him.

The first psychiatric hospitalization

After about 20 days of staying in community, our Patient presented such a dangerous aggressive behaviour against another boy who lived in the community, as to be hospitalized in a psychiatric ward. He was discharged after a few days, and sent to the psychiatric ward dedicated to adolescent patients in a private hospital, where he remained hospitalized for about 3 months. During this hospitalization, many clinical features of PWS emerged, in particular hyperphagia and severe behavioural alterations, characterized by outbursts of anger and violence toward objects and people. WAIS was administered to him, where he obtained a score of 68 on verbal IQ scale and 62 on performance IQ scale On the Vineland scale, the patient showed a result consistent with mild mental impairment.

The first rehabilitative program

At discharge from the private psychiatric hospital, he was sent back to his adoptive family with a rehabilitation program, which provided for daily attendance at the rehabilitative centre of a mental disability facility. Clinical conditions of the Patient remained stable for 5 months. Afterwards, he was again hospitalized in the public acute psychiatric ward due to agitation and aggressiveness, apparently motivated by frustration for being scolded by

both professionals and parents for his "sentimental effusion" towards a female patient who attended the same rehabilitative centre. After few days, he was discharged and sent to the adult outpatient psychiatric services since he had come of age.

The long psychiatric hospitalization

A few days after previous hospitalization, he was re-admitted to the same acute psychiatric ward, due to an outburst crisis at the rehabilitative centre, reactive to the attempts of professionals to control his dangerous abuse of water. He binged daily on water, especially at lunch time, in response to rigid reduction of food intake. During this hospitalization, the Patient presented dangerous behaviour: abuse of water, theft of food from other patients (also leftovers from dishes or rubbish bins) and theft of money to buy food. In particular, he remained awake at night to go hunting for food and money in the rooms of other patients. The Patient also used to hoard stolen food in some hiding places on the ward (including in the toilet bowl), where he went to eat food unseen. When he was discovered committing these acts as well as when he was prohibited eating more than his regulated diet, he became extremely aggressive with explosive and unstoppable violence against people and objects surrounding him. It was necessary to pharmacologically and physically restrain him repeatedly. During this long hospitalization, mother, who, in the meantime, was nominated his legal guardian, referred not to be available to take him home again due to his dangerous behaviour, which she and her husband were not able to contain. She asked to place the Patient in a rehabilitative facility in order to modify his behaviour. After a month of hospitalization, the Patient presented aggressiveness frequently difficult to contain as well as uncontrollable food intake (he had gained about 10 kg since admission), although he continued his daily rehabilitative activities in an outpatient service. Therefore, a multi-professional meeting planned to transfer the Patient to a residential rehabilitative facility (RRF) for people with disabilities, and to dedicate professionals to him 24 h a day, at least in the beginning of the program.

Rehabilitation in the residential facility

At admission to the RFF, a complex and intensive program which provided maximum control over food intake and, at the same time, various physical activities and recreations, was tailored for the Patient.

A. Control of food intake. A low-fat diet with MCT (medium-chain triglyceride) of 1700 kcal/day, divided into three main meals and two snacks, one in the morning and one in the afternoon, was provided; the Patient was not allowed to consume morning and afternoon snacks with other patients, having a dietary restriction that others did not have and other many prohibitions related to food were established (no access to the kitchen pantry day or night, no change to the timing of meals in order to maintain regular life habits, no using food as bargain or as reward or punishment in order to reduce positive reinforcement by food).
B. Motor activities. An intensive program was carried out, under the constant supervision of educators, which included physical activities and games: gymnastics with a frequency of four times a week at the RRF gym, soccer play with the other guests and swimming in the pool once a week; physical activity under teacher supervision at a gym once a week. During the rest of the time, the Patient was encouraged to walk as much as possible by the operator dedicated to him in order to counteract the tendency to weight gain and, at the same time, to distract him from the compulsive search for food.
C. Activities aimed at improving socialization and autonomy capacity. Many organized recreational activities were planned: visits to farms, libraries, playgrounds, leisure centres, etc., together with other patients who lived in the RRF and with professionals dedicated to him. Regarding money management, educators received money from Patient's mother, his legal guardian, and delivered money to him, according to some clear rules: he could receive a certain sum to buy only one item during the weekly recreational walk (food purchase was not allowed). In this regard, the Patient had to previously agree with the educator on the item to buy, through a written agreement signed by both parties, and could not change his choice.

During his stay at the residential facility, the patient also continued to be seen regularly by his referring psychiatrist. In these meetings, the Patient revealed his feelings of inadequacy, anxiety, anger and fears. He complained to be suffering due to "the insatiable desire for food" and "attraction towards girls". All visits ended with the same incessant requests to be admitted to the public psychiatric hospital, where the patient felt "less controlled". A new psychotherapy for the Patient was carried out by a psychologist from the Prader-Willi Association, focusing on the Patient's feelings of abandonment by his adoptive mother and his difficulties with others. The Patient was also monitored monthly by the general physician of the RRF, who regularly checked his physical condition (body weight, hematic tests). He was periodically visited by endocrine and nutrition specialists.

The assessment of outcomes

The number of psychiatric hospitalizations during the observation period

After 3 months, the Patient was again admitted to the public psychiatric hospital because of his hostile and threatening behaviour. After his admission, he immediately appeared sufficiently quiet and cooperative as to be promptly discharged and sent back to the RRF in order to continue his program. After another 6 months, he presented a new crisis for the "loss" of his adoptive family requiring compulsory psychiatric hospitalization, due to uncontrollable outbursts of anger and violence. After 7 days, he was discharged to resume his rehabilitative program. Successively, in concomitance with the summer holidays of his referring professionals, momently substituted by other ones, and the reduction of his recreational activities, he presented a progressive increase of dangerous behaviour. In that period, he had physically assaulted a professional, causing him an arm fracture; he had removed the cannula for parenteral nutrition from the body of another patient, in a vain attempt to feed by it; he had repeatedly ingested earth and grass gathered from the garden of the institute and so on. Finally, the Patient was admitted again to the public psychiatric ward, where he presented violence against himself, motivated by the frustration of not being able to eat freely despite his insatiable hunger. In the ward, he was isolated from other patients and controlled 24 h a day by one of the professionals dedicated to him. This intensive control permitted his rapid tranquillization and, consequently, his discharge after few days. He was again sent to the RRF, where he continued his program with new activities: he began a protected work project in an outside rehabilitative centre for 2 h once a week. At this centre, the Patient performed small manual tasks such as assembling and packaging items, under the constant supervision of his professionals, and earned a monthly salary. In the meantime, his adoptive mother reduced her visits to him to no more than once a month hoping to reduce the patient's tantrums, whereas his biological sister, who lived in the same adoptive family, progressively increased her visits, accompanying him out for walks and home visits. The Patient, who looked forward to going back to his family, presented appropriate behaviour during his monthly authorized home visit, reporting great satisfaction. Successively, he was not hospitalized, showing a progressive improvement in his behaviour with good adaptation to the RRF. As shown in Fig. 1, the days of hospitalizations were significantly reduced to zero at the end of the observation period, fulfilling one of the main outcomes of his rehabilitation program.

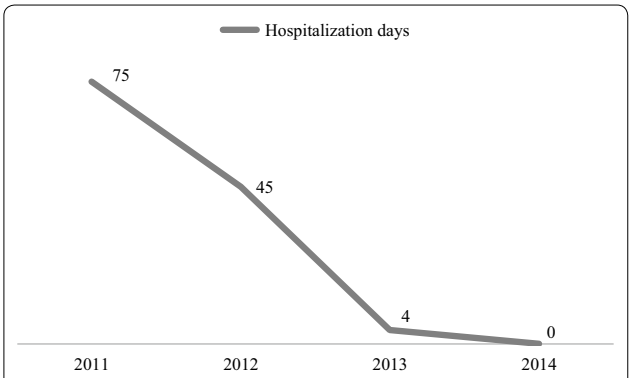

Fig. 1 Days of psychiatric hospitalizations during the observation period

Pharmacological therapies

The patient was treated with neuroleptics and benzodiazepines due to his severe behavioural alterations, despite the risk for increased appetite. At the initial admission to the RRF, he was treated with 30 mg of aripiprazole and 1500 mg of valproic acid, but after a few weeks, valproic acid was suspended due to its inefficacy to control aggressiveness. During the observation period, the patient frequently required additional sedative therapies for his severe behavioural alterations, like chlorpromazine (100 mg/day) and benzodiazepines (alprazolam 3.5 mg/day, clordemetildiazepam 2mg/day, lorazepam 4 mg/day). The patient had never been prescribed hormonal therapy (growth hormone or testosterone), which was not considered useful by endocrinologists who examined him, given the risk of worsening his behavioural problems.

The scale scores

"VADO": (a) Specific outcome (Fig. 2), which consisted of avoiding psychiatric hospitalizations, pathologically required by the Patient, was achieved an improvement rate of 63 %; (b) Rehabilitation Areas (Fig. 3), which evaluated the Patient's adherence to different rehabilitation activities, showed an improvement rate of 51 %; (c) Personal and Social Performances (Fig. 4), which evaluated the Patient's ability to take care of his personal hygiene and clothing, showed an improvement of 61 %.

"Personal and Social Performance Scale" (PSP) reported an overall improvement of 44 % at the end of the observation period, with the highest percentage of improvement (60 %) in his disturbing and aggressive behaviour (Fig. 5).

Body mass index (BMI)

At the initial admission to the RRF, the patient presented a BMI of 33.9 (weight 90 kg, height of 1.63 cm), higher than the normal value of 24.9. At the end of the observation period, he had a BMI of 32.8, despite the strictly controlled diet and regular physical activity (Fig. 6).

During all internist visits, any significant organic complications were registered; in particular any sign of

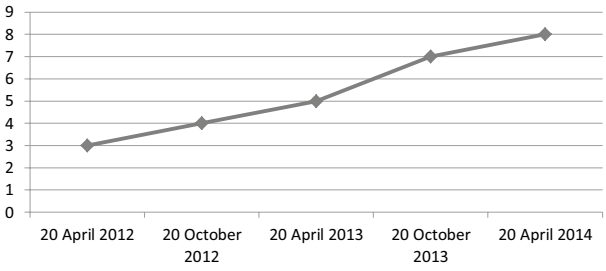

Fig. 2 "VADO": Specific outcome

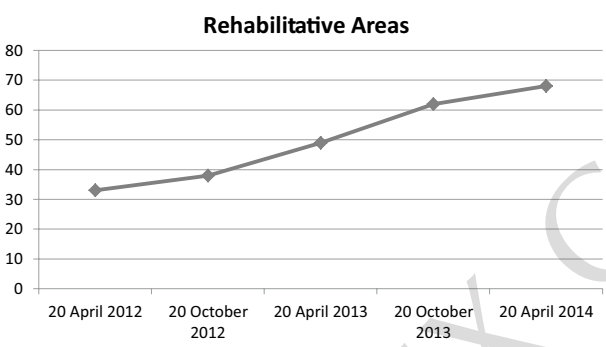

Fig. 3 "VADO": Rehabilitation Areas

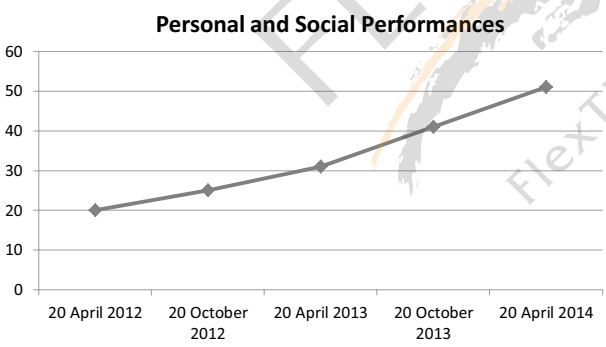

Fig. 4 "VADO": Personal and Social Performances

hypothyroidism or diabetes mellitus was noted. All his hematic tests were mostly normal.

Current state update

To date, the patient continues his rehabilitation activities at the RRF, with good cooperation despite some moments of anger and aggression that his professionals are able to contain without resorting to psychiatric hospitalization. He follows his usual hypocaloric diet with no extras and, at the last control, he weighed 87 kg (BMI = 32.74) with normal hematic test. Ultimately, he shows an increased interest in hoarding different non-food items such as toy soldiers, comics, horror movies, crossword puzzles, etc., all activities which are allowed in the RRF, suggesting that he maintains compulsive behaviour although directed on different objects from food.

Conclusion

In our PWS case, psychiatric intervention was necessary because of his severe mental and behavioural alterations: aggressiveness, mental retardation, outbursts of anger, disruptive crisis, obsessive and compulsive behaviour. These symptoms, related to the genetic disorder, had probably been exacerbated by early abandonment by his biological parents and, successively, by the difficulty his adoptive family had in caring him. In line with most studies [2, 27, 28], our case shows that a genetic syndrome can impair individual's essential needs, leading to severe maladjustment. This condition requires a bio-psycho-social approach in order to take care of both organic conditions and psychological needs without neglecting the environmental conditions.

The psychiatric intervention was closely connected with well-structured rehabilitation programs at the RFF, which stimulated Patient's capabilities, despite his initial poor self-management skills, and, in the meantime, controlled his behaviour by the regular daily presence of one of the three professionals dedicated to him. This continuous and intense rehabilitation program has led to a significant reduction of hospitalizations, allowing the Patient to avoid the behavioural regression induced by frequent and recurrent admissions, at the cost of an increased dependence on institutions. Despite these positive results, the weight control induced only a slight reduction in BMI, maintaining it within the range of moderate obesity at the end of the observation period. Nevertheless, this result obtained through an enormous rehabilitative and educational effort by the RRF staff, represented a good outcome since further weight gain, which is the common final pathway in most PWS, was avoided. The data show that obesity related to genetically induced hyperphagia can be controlled by a regular and long-term rehabilitative approach tailored to behavioural and psychological alterations. At the RRF, body weight control was carried out 24 h a day through the adoption of different strategies aimed at controlling of food intake and, in the meantime, at reinforcing all activities without any oral gratification. At the end of the observation period, the staff registered a significant improvement in the rehabilitation areas of his personal and social functioning, whereas his referring psychiatrist found most

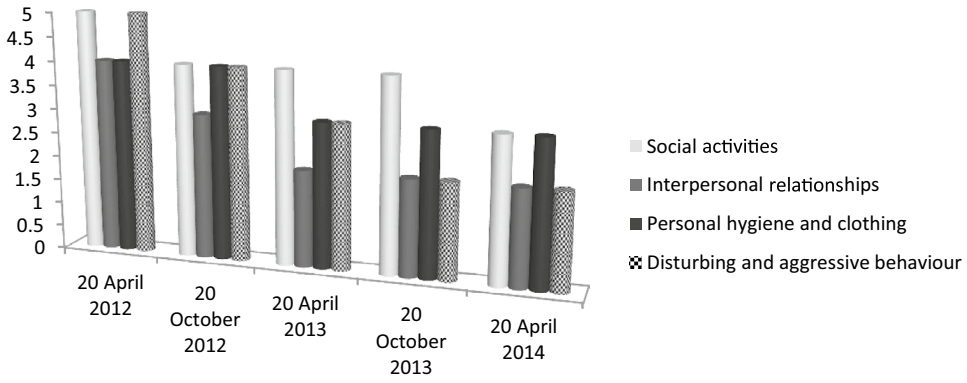

Fig. 5 The main areas of Personal and Social Performance (PSP) scale

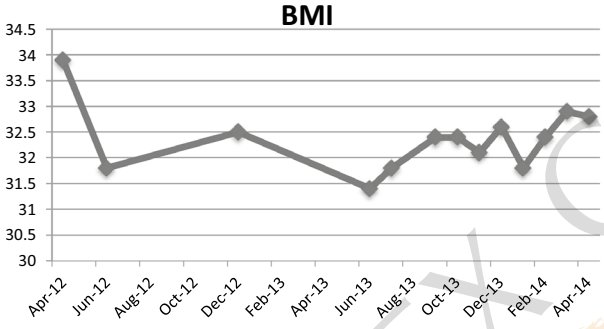

Fig. 6 Body mass index (BMI) during the observation period

relevant the reduction of his disturbing and aggressive behaviour.

Finally, the clinical observation of this case leads us to compare PWS to drug addiction and indirectly endorse the neurophysiological hypothesis that food and drugs stimulate the same brain circuits in the limbic system [15]. In this regard, many symptoms presented by our Patient, such as impulsivity, craving for food, compulsive overeating and obesity support the concept of food addiction, first developed by Gold's team [29] and successively interpreted as a Reward Deficiency Syndrome by other authors [30], suggesting a commonality between substance and behavioural addiction. Food addiction, which shares with substance abuse and gambling DSM-5 criteria and brain reward networks, is characterized by craving, as well as other addictions, which, in this case, is for food [31]. Other studies have shown that obese populations with greater BMI present changes in reward pathways similar to those observed in drug addiction. In particular, some research has found that, in individuals with higher BMI, dopaminergic receptors are down-regulated [32] and present greater activation in the gustatory cortex and somatosensory brain regions in the presence of food [33]. Other genetic studies have confirmed biological predisposition to overeating and weight gain, indicating that genetic polymorphism of dopamine D2 receptor and leptin receptor genes are involved in obesity and craving for food [34, 35]. PWS could represent an extreme case biologically conditioned, which could help us to better understand the complex pathophysiological mechanisms that underlie both addiction and obesity. Most studies underline that effective treatments for drug addiction and obesity can be different since the modality of relapse is not similar [36]. Some authors have indicated that a pharmacological strategy aimed at improving dopamine functioning could be effective for both diseases, but, up to now, the results are inconclusive. Nevertheless, due to the complexity of addiction and obesity, which can be strongly influenced by environmental factors, behavioural therapeutic programs aimed at improving the capacity of the individual to control on his/her compulsive behaviour by means of positive reinforces can be effective.

Our clinical case, emblematic for its complex therapeutic and rehabilitative needs, required a multidisciplinary staff since many different activities, ranging from control of organic symptoms to educational and rehabilitation programs, were necessary to manage his multiple symptoms. Nevertheless, an empathic relationship, despite Patient's manipulative and aggressive attitudes, was necessary to motivate and support him in the course of such a difficult treatment. Although the genetic component heavily influenced the course of this disorder, we can highlight that a long-term, well-defined and individualized rehabilitative program can control pathological behaviour, including hyperphagia, and therefore improve the long-term prognosis. In order to implement these programs, emphatic therapeutic relationships are necessary in order to support and motivate patients in adhering to rehabilitative programs, the only available treatment preventing potential regressive evolution.

Postural adaptations to long-term training in Prader-Willi patients

Abstract

Background: Improving balance and reducing risk of falls is a relevant issue in Prader-Willi Syndrome (PWS). The present study aims to quantify the effect of a mixed training program on balance in patients with PWS.

Methods: Eleven adult PWS patients (mean age: 33.8 ± 4.3 years; mean BMI: 43.3 ± 5.9 Kg/m2) attended a 2-week training program including balance exercises during their hospital stay. At discharge, Group 1 (6 patients) continued the same exercises at home for 6 months, while Group 2 (5 patients) quitted the program. In both groups, a low-calorie, well-balanced diet of 1.200 kcal/day was advised. They were assessed at admission (PRE), after 2 weeks (POST1) and at 6-month (POST2). The assessment consisted of a clinical examination, video recording and 60-second postural evaluation on a force platform. Range of center of pressure (CoP) displacement in the antero-posterior direction ($RANGE_{AP}$ index) and the medio-lateral direction ($RANGE_{ML}$ index) and its total trajectory length were computed.

Results: At POST1, no significant changes in all of the postural parameters were observed. At completion of the home program (POST2), the postural assessment did not reveal significant modifications. No changes in BMI were observed in PWS at POST2.

Conclusions: Our results showed that a long-term mixed, but predominantly home-based training on PWS individuals was not effective in improving balance capacity. Possible causes of the lack of effectiveness of our intervention include lack of training specificity, an inadequate dose of exercise, an underestimation of the neural and sensory component in planning rehabilitation exercise and failed body weight reduction during the training. Also, the physiology of balance instability in these patients may possibly compose a complex puzzle not affected by our exercise training, mainly targeting muscle weakness.

Background

Prader-Willi syndrome (PWS) is the most frequent cause of syndromic obesity and occurs in 1 in every 25,000 live births [1]. Its major clinical features include muscular hypotonia, childhood-onset obesity, short stature, small hands and feet, scoliosis, osteoporosis, hypogonadism and developmental delays [2]. Hyperphagia and weight gain between the ages of 1 and 6, lead most PWS patients to develop morbid obesity, affecting the development of motor and functional skills [3]. In adult life, although hypotonia does not progress, the progressive effects of obesity on the joints produce a cautious abnormal gait [4,5]. PWS patients present with reduced lean body mass and increased fat to lean mass ratio not only when compared with lean patients but also in relation to obese patients [6,7].

In general, obese individuals are typically sedentary as there is an inverse relationship between BMI and activity levels [8]. An increase in BMI is also associated with an increase in functional impairment [9], which could lead to impaired balance and an increased risk of falls than normal-weight individuals under daily postural stresses and perturbations [10,11], even in younger individuals, under 40 years of age [12,13]. Consequently, obese individuals may fear falling, which may lead to further reductions in physical activity [8], greater functional impairment [14], and greater risk of falling.

Obesity associated with PWS is often massive and many individuals exceed by more than 200% their ideal body weight. In addition to that and muscular hypotonia, PWS show dysmorphic features that can affect postural stability, as short stature, small hands and feet, scoliosis and in fact they show a poorer balance capacity than their non-genetically obese counterparts [15]. It is therefore not surprisingly that fracture risk is approximately 50% in children [16] and more than 30% in adults [17]. The issue of whether rehabilitation interventions may improve balance and decrease risk of fall in PWS appears therefore certainly clinically relevant.

In a previous study [15], we demonstrated that PWS patients have a poorer balance capacity than their non-genetically obese counterparts and our findings suggested that strengthening of ankle flexors/extensors, balance training and tailored exercises aimed at improving medial-lateral control using hip strategies should be given particular consideration within rehabilitation programs.

Benefits from specific posture programs designed to improve balance and strength have been documented in obese patients [18], and weight reduction programs have a favorable impact on posture instability [13]. Maffiuletti et al [12] investigated the effect of a 3-week weight reduction program plus specific balance training on postural stability in extremely obese individuals. They demonstrated that a weight reduction program associated with a specific balance training was significantly more effective than the first alone. To our knowledge, no studies have quantitatively evaluated the effects of a training program on balance in PWS patients.

Vismara et al [19] have demonstrated that long-term group interventions (6 months) are feasible in PWS, despite their particular psychological profile, and effective in improving muscle strength and gait strategy.

The aim of this investigation was therefore to evaluate the effectiveness of a mixed exercise program, partially supervised and partially home-based, on postural stability in PWS adults.

Methods

Participants

We enrolled 11 adult patients with PWS (age: 33.8 ± 4.3 years; BMI: 43.3 ± 5.9 kg/m2) admitted to our rehabilitation hospital. Physical examination included determination of height and weight under fasting conditions and after voiding. BMI was defined as weight/height^2 (kg/m^2). All patients showed the typical PWS clinical phenotype [20]. Cytogenetic analysis was performed in all participants; 10 had interstitial deletion of the proximal long arm of chromosome 15 (del15q11-q13). Moreover, uniparental maternal disomy for chromosome 15 (UPD15) was found in 1 female.

All PWS subjects showed mild mental retardation. One of the admission criteria for the study was a score over the cut-off value of 24 in the Mini Mental State Examination (MMSE) Italian version [21]. Scores over the MMSE cut-off suggest the absence of widespread acquired cognitive disorders in adult people. Our PWS patients were all able to understand and complete the testing.

The control group included 20 healthy individuals (CG: 10 females and 10 males; BMI: 21.6 ± 1.6 kg/m2; age: 30.5 ± 5.3 years). All participants were free from conditions associated with impaired balance. We clinically examined the experimental subjects to exclude individuals with vision loss/alteration, vestibular impairments, neuropathy and those who reported symptoms related to intracranial hypertension. All PWS and CG had normal values in the main laboratory tests, including adrenal and thyroid function. The study was approved by the Ethics Research Committee of the Institute. Written informed consent was obtained by patients, where applicable or their parents.

Intervention

On admission, all patients underwent a clinical assessment. During their hospital stay, they attended a 2-week training program which included supervised exercise sessions with specific muscle strengthening of the lower limbs and 30-45 min aerobic walking sessions. All these sessions were held 4 days per week and included an introductory talk aimed at educating patients about the obesity-related changes in gait and posture and at providing practical information about their rehabilitation program. The sessions consisted of 4 exercises, explained as follows:

1) “Stand up against the wall without letting your heels touch it, bend at your knees to 90° as if you were about to sit down, then slowly return to the upright position";
2) “Stand up against the wall and then alternately lift your toes upwards";
3) “From a standing position, raise yourself up onto your toes and then slowly lower your heels back to the ground";
4) “Walk on your heels at a comfortable speed and don’t let the rest of your feet touch the floor”.

For exercises 1, 2, and 3 patients were asked to complete 3 sets of 15 repetitions each. For exercise 4, patients were asked to walk approximately 4 metres and then repeat the task 10 times with a rest in-between.

They were instructed to perform the exercise program at home 3 times a week for 6 months. Patients were required to keep a daily record of their adherence to the program.

At discharge, Group 1 (6 patients) continued the same 4 exercises unsupervised at home for 6 months, while Group 2 (5 patients) did not undergo the training program, according to a deliberate experimental design. In all subjects, a low-calorie, well-balanced diet of 1.200 kcal/day was advised during hospital stay and the 6-month home-training. Historically, the calorie requirement to maintain weight in adults with PWS is about 60% of normal, and a low calorie, well-balanced diet of 1,000-1,200 kcal/day combined with regular exercise should be advised [22]. Furthermore, a general recommendation to obtain weight loss has been from 800 to 1.000 kcal/day. In this light, adherence to these calorie-restricted diets requires intensive and continuous monitoring of intake by caregivers and regular dietary counselling.

Methods

Subjects were assessed on admission (PRE), at discharge after 2 weeks (POST1) and after the 6-month training program (POST2). The assessment consisted of a clinical examination, video recording and postural evaluation.

The postural evaluation was conducted with a force platform (Kistler, CH; acquisition frequency: 500 Hz) integrated with a video system. The output of the force platform are three orthogonal components of ground reaction force (F_{ML}, i.e. the component of ground reaction force in the medio-lateral direction, F_{AP}, i.e. the component of ground reaction force in the antero-posterior direction; F_V, i.e. the component of ground reaction force in vertical direction), a torsion moment, and the coordinate of Centre of Pressure (CoP) (CoP_{ML}, i.e. the component of CoP displacement in the M/L direction and CoP_{AP}, i.e. the component of CoP displacement in the A/P direction) on the horizontal plane.

The individuals were instructed to maintain an upright standing position for 60 seconds with open eyes (OE) focusing on a 6 cm black circle positioned at the individual line of vision at a distance of 1.5 m. Arms were hanging by their sides and feet were positioned at an angle of 30° with respect to the A/P direction. To standardize the experimental position, a triangle was located between the feet and removed just before acquisition. To avoid any kind of learning or fatigue effect [23] only one trial was acquired in this study for each session.

Data analysis

The outputs of the force platform allowed us to compute the CoP time series in the A/P direction (CoP_{AP}) and the M/L direction (CoP_{ML}). The first 10s interval was discarded in order to avoid the transition phase in reaching the postural steady state [24].

In accordance with the literature [11] the following parameters were computed as significant for the postural analysis:

- RANGE: the range of CoP displacement in the A/P direction ($RANGE_{AP}$ index) and the M/L direction ($RANGE_{ML}$ index), expressed in mm;
- Sway Path (SP): the total CoP trajectory length, expressed in mm.

All parameters were normalized to the participant's height (expressed in meters), according to literature [25], in order to avoid the influence of different subject's height on the results.

Statistical analysis

All the previously defined parameters were computed for each participant and then the mean values and standard deviations of all indexes were calculated for each sessions in PWS and for CG. Data of all patients were compared using Wilcoxon matched pair test, to detect significant PRE-POST1 differences; the same test was used to compared POST1 and POST2 of Group 1 and Group 2, considering each group separately. PWS and CG data were compared with Mann-Whitney U tests. Null hypotheses were rejected when probabilities were below 0.05.

Results

In Table I, mean and standard deviation values for each postural parameter are displayed at PRE and POST1 for PWS and CG. The reported values were normalised for individual height (expressed in meters).

At PRE, the analysed parameters were statistically different in PWS and CG, suggesting that PWS patients did not present a physiological postural strategy. PWS individuals showed greater displacements along both the A/P and the M/L direction in terms of RANGE, in line with previous observations [12], and a longer SP than CG.

At POST1, no significant changes were observed in all of the parameters (Table 1) and BMI was similar to those observed at PRE session (43.04 ± 7.43 kg/m^2).

At POST2, Group 1 (6 patients, undergoing the rehabilitative treatment at home for 6 months) and Group 2

Table 1 Postural parameters of PWS at PRE and POST1

	PRE	*POST1*	*CG*
$RANGE_{AP}$	19.04 (6.76)*	17.67 (5.24)*	5.03 (2.65)
$RANGE_{ML}$	14.79 (9.53)*	12.59 (5.21)*	9.36 (3.53)
SP	573.58 (86.19)*	513.03 (80.90)*	201.33 (45.86)

Data are expressed as mean (standard deviation) (expressed in mm) and are normalised to the participant's height (expressed in meters). CG: Control group. * = $p < 0.05$, PRE and POST1 versus CG.

(5 patients, non exercising after the completion of the 2-week supervised program) were compared. The adherence to the home-based program, computed as the percentage of number of sessions performed/number of total sessions, was 90%. The postural condition of both groups of PWS patients were unchanged (Figure 1, Figure 2), maintaining the higher values for $RANGE_{AP}$ and $RANGE_{ML}$ parameters. The SP did not differ significantly both in GROUP1 (498.74 ± 70.26 vs. 469.53 ± 58.67; $p > 0.05$) and in GROUP2 (527.32 ± 91-18 vs. 506.63 ± 90.92; $p > 0.05$), too.

At POST2, BMI was similar to those observed in basal condition both in GROUP1 (40.38 ± 3.46 kg/m^2 vs. 42.57 ± 4.92 kg/m^2; $p > 0.05$) and in GROUP2 (42.54 ± 7.69 kg/m^2 vs. 38.35 ± 2.13 kg/m^2; $p > 0.05$).

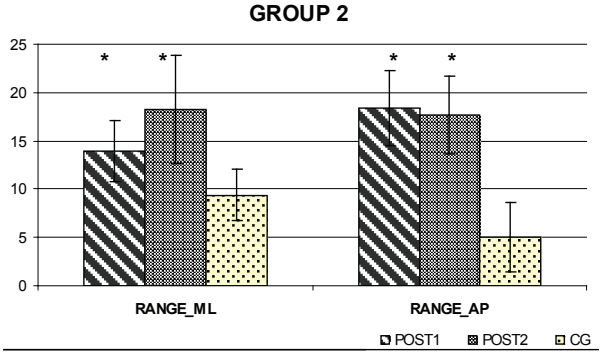

Figure 2 Postural parameters of GROUP2 at POST1 and POST2. Data are expressed as mean (standard deviation) (expressed in mm) and are normalised to the participant's height (expressed in meters). CG: Control group. * = $p < 0.05$, POST1 and POST2 versus CG.

Discussion

The issue of whether rehabilitation interventions may improve balance and decrease risk of fall in PWS certainly appears clinically relevant. PWS patients are characterized by an increase in BMI which is demonstrated to be associated with an increase in functional impairment [9], which could lead to impaired balance and an increased risk of falls. As obese individuals generally fear falling, further reductions in physical activity [8], greater functional impairment [14], and greater risk of falling may occur.

Based on a recent study of our group on PWS [19] showing that long-term strengthening and gait training is feasible and effective, with the present investigation we aimed to verify if the reduced balance could be amended by specific training. For PWS, providing an effective and simple home-based training would represent a continuum of the rehabilitation process outside the hospital which appears crucial in all chronic conditions. Given the psychological profile of PWS individuals, training sessions should be kept simple and reasonably short to guarantee compliance to the program. The exercises we prescribed were simple, clearly explained and did not exceed a total of 30 min/day. Also, patients had been previously familiarized with the exercises and supervised for 2 weeks in order to make sure they would be able to perform them properly at home in the following 6-month training period.

Our initial hypothesis was that balance is mainly reduced in PWS because of muscle weakness [7] and our training addressed the muscle groups that had been found to be mainly responsible for gait disorders [5]. In particular our training focused on ankle flexor and extensor muscle groups but did not include specific balance and proprioceptive exercises. A main reason for that was to provide simple and repetitive exercises, confined in a limited lapse of time, to be safely rehearsed by the patients at home. Adding diverse exercises might have jeopardized compliance in patients who psychologically need reassuring repetitive tasks.

Unfortunately, our results suggest that, unlike our previous positive results in strength gain and gait improvement [19] and despite a high adherence to the program, no postural adaptations occur after a long-term, mainly home-based strength training of the lower limb muscles. We have chosen this type of intervention on the basis of the known reduced muscle tonus and strength in PWS, which have been acknowledged as major causes of poorer balance.

A possible bias of our study is the relatively small sample size, although it should be reminded that PWS is a rare condition and large experimental groups are difficult to gather. As overweight is a distinctive feature in PWS, the analysis should have been more rigorously compared with obese instead of normal-weight individuals. However, the main object of our investigation was to assess quantitatively the effect of a mixed

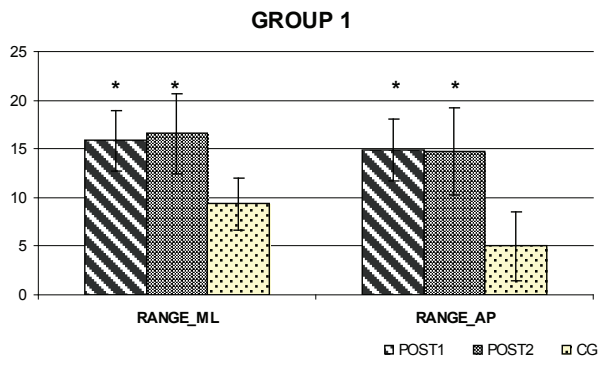

Figure 1 Postural parameters of GROUP1 at POST1 and POST2. Data are expressed as mean (standard deviation) (expressed in mm) and are normalised to the participant's height (expressed in meters). CG: Control group. * = $p < 0.05$, POST1 and POST2 versus CG.

training program on balance in patients with PWS. Also, the low intensity of the home-based program may have played a role in the negative results. Although exercise intensity at home was not measured, anti-gravity resistance exercises in subjects with an excess in body mass should provide adequate exercise intensity for the aim of improving function. Intensities as low as 60% of the maximum voluntary contraction have indeed proved to be an effective stimulus for strength and function gain in elderly subjects [26]. Apart from muscle weakness, the control of stability and posture requires a complex interaction of both the musculoskeletal and neural system. Balance capacity is also secondary to body alignment and muscle tone. The first factor can in fact minimise the effect of gravitational forces while the second counteracts gravity. Postural tone is fine tuned, among other factors, by intrinsic stiffness of the muscles and neural drive. Sensory/perceptual processes, involving the organisation and integration of visual, vestibular and proprioceptive systems also play a role. It can be speculated that our exercise program may have lacked of specificity with regard to balance and oversimplified the functions to be trained, mainly targeting muscle strengthening and sensory-motor integration. Also, the dose of exercise, in terms of intensity and duration of the program, could represent a possible cause of the lack of effectiveness of the training.

Our results are in contrast with those obtained by Maffiuletti et al [12] on morbidly obese individuals. In their study, specific balance training, in addition to a body weight reduction program, improved significantly the postural strategy of these patients. In our study, training was indeed associated to the administration of a hypocaloric diet, but weight reduction is difficult to achieve in adults PWS due to their insatiable appetite and food-seeking behavior. It could be speculated that weight loss in addition to specific balance training is mandatory in order to improve balance capacity in PWS.

Baseline postural capacity is different in the two populations, with PWS patients generally characterized by poorer balance than their non-genetically counterparts. The mechanisms underlying this reduced capacity have not been thoroughly investigated in PWS. Future research will need to address quality and quantity of exercises targeted at improving balance capacity in PWS as well as to unveil the physiological determinants of instability in PWS.

Conclusions

In this study we evaluated quantitatively the effectiveness of a mixed exercise program, partially supervised and partially home-based, on postural stability in PWS adults. Our results suggest that no postural adaptations occur after this program, unlike our previous positive results in strength gain and gait improvement and despite a high adherence to the program. Probably the low dose of intensity of exercise, in terms of intensity and duration of the program, associated to the lack of specific balance training may have played a role in the negative results and could represent a possible cause of the lack of effectiveness of the training.

These results are important from a clinical and rehabilitative point of view as they suggest the need of enhancing quality and quantity of exercises targeted at improving balance capacity in PWS patients.

Gait initiation and termination strategies in patients with Prader-Willi syndrome

Abstract

Background: Gait Initiation (GI) is a functional task representing one of the first voluntary destabilizing behaviours observed in the development of a locomotor pattern as the whole body centre of mass transitions from a large to a small base of support. Conversely, Gait Termination (GT) consists in the transition from walking to standing which, in everyday life, is a very common movement. Compared to normal walking, it requires higher control of postural stability. For a safe GT, the forward movement of the body has to be slowed down to achieve a stable upright position. Stability requirements have to be fulfilled for safe GT. In individuals with Prader-Willi syndrome (PWS), excessive body weight negatively affects the movement, such as walking and posture, but there are no experimental studies about GI and GT in these individuals. The aim of this study was to quantitatively characterise the strategy of patients with PWS during GI and GT using parameters obtained by the Center of Pressure (CoP) track.

Methods: Twelve patients with PWS, 20 obese (OG) and 19 healthy individuals (HG) were tested using a force platform during the GI and GT tasks. CoP plots were divided into different phases, and duration, length and velocity of the CoP trace in these phases were calculated and compared for each task.

Results: As for GI, the results showed a significant reduction of the task duration and lower velocity and CoP length parameters in PWS, compared to OG and HG. In PWS, those parameters were reduced to a higher degree with respect to the OG. During GT, longer durations, similar to OG, were observed in PWS than HG. Velocity is reduced when compared to OG and HG, especially in medio-lateral direction and in the terminal part of GT.

Conclusions: From these data, GI appears to be a demanding task in most of its sub-phases for PWS individuals, while GT seems to require caution only towards the end of the task. Breaking the cycle of gait into the phases of GI and GT and implementing specific exercises focusing on weight transfer and foot clearance during the transition phase from the steady condition to gait will possibly improve the effectiveness of rehabilitation and fall and injury prevention

Keywords: Gait initiation, Gait termination, Prader-Willi syndrome, Obesity, Rehabilitation, Center of pressure

Background

There is now a body of literature on various "sub-tasks" of walking that may compromise stability, such as initiation, termination, turning, obstacle crossing, negotiating a raised surface and stair climbing. In all these tasks balance is challenged during the transition from one, either statically stable or dynamically stable movement pattern, to another [1]. However, limited focus has been placed on gait initiation and termination. The dynamic processes of gait initiation and termination are much more complex since the human body needs to accelerate and decelerate, respectively, often in a limited amount of time. As a result, the skills necessary to maintain stability, weight transfer, foot clearance, etc., become more critical during these transition phases than during the steady state conditions [2, 3]. Such requirements become even more significant in patients with neurological disorders, lower limb complications, and in older adults, where there are inherent difficulties with postural stability and gait [4, 5].

In particular, gait initiation (GI) represents the transition from standing to walking, it is a task that is often required in daily life and challenges balance control [6, 7].

Compared to steady-state walking, the requirements on the neuromuscular system are increased in GI, since a complex integration of neural mechanisms, muscle activity and biomechanical forces is necessary [6]. GI is a functional task representing one of the first voluntary destabilizing behaviours observed in the development of a locomotor pattern as the whole body centre of mass (COM) transitions from a large to small base of support (from a bipedal to a monopedal position related to gait). This task represents a challenge to the postural control system due to the volitional transition from a condition of relatively static stable support to one of continuously unstable posture during locomotion [8–11] and one that has been shown to be a sensitive indicator of balance dysfunction [11].

Conversely, gait termination (GT) consist in the transition from walking to standing that, in everyday life, is a very common movement [12]. Compared to normal walking, it requires higher control of postural stability and a complex integration and cooperation within the neuromuscular system [6, 13, 14]. For a safe GT, the forward movement of the body has to be slowed down to achieve a stable upright position [13, 15]. Stability requirements have to be fulfilled for safe gait termination. In the final bipedal standing position, the COM coincides with the Centre of Pressure (CoP) and lies within the base of support [16, 17].

These two motor tasks have been studied to provide insight into dynamic postural control and the changes that occur in the control system only with advancing age and disability, such as in individual with Parkinson, individual with multiple sclerosis, obeses and individuals with lower limb amputation [1, 7, 9, 18–28]. To the best of our knowledge, no studies on GI and GT in patients with Prader-Willi syndrome (PWS) have been published so far. Prader-Willi syndrome (PWS) is the most frequent cause of syndromic obesity with an estimated prevalence of 1:10.000/30.000 [29]. Its major clinical features include muscular hypotonia, childhood-onset obesity, short stature, small hands and feet, scoliosis, osteoporosis, hypogonadism and developmental delays [30]. Typically, PWS patients present with reduced lean body mass and increased fat to lean mass ratio not only when compared with lean patients but also in relation to obese patients [31, 32]. Obesity and excessive amounts of fat modify the body geometry by adding passive mass to different regions and influence the biomechanics of activities of daily living, causing functional limitations, and possibly predisposing the patient to injury. Quantitative evidence exists that excessive body weight negatively affects the movement from sitting to standing and walking in obese [33] and in PWS individuals [34]. Body mass increases can also be a major factor contributing to the occurrence of falls, which explains why obese persons appear to be at greater risk than normal-weight individuals under daily postural stresses and perturbations [35, 36].

According to these considerations, patients with PWS may cope with more difficulty with GI and GT demands. Previous papers have addressed the poor balance [37, 38] and gait difficulties [34, 39] in individuals with PWS, unveiling the motor abnormalities related both to an excessive body mass under static and dynamic conditions and to some dysmorphic features, as short stature, small hands and feet, scoliosis and muscular hypotonia. Given that GI and GT could be destabilizing activities for PWS patients, the purpose of this study was to quantitatively characterise the strategy of these individuals during these tasks using parameters obtained by the Center of Pressure (CoP) track. The results were compared with those obtained in a group of non-genetically obese subjects and in a group of normal weight subjects.

Methods

Participants

In this study, 3 groups of participants were recruited. Twelve adult patients (7 females, 5 males; age: 36.6 ± 6.6 years; height: 1.57 ± 0.04 m; BMI: 38.1 ± 6.9 kg/m^2) with a diagnosis of PWS were enrolled in this study. The PWS patients had been periodically hospitalized at the San Giuseppe Hospital, Istituto Auxologico Italiano, Piancavallo (Verbania), Italy. During hospital stay, patients undergo a 4-week multidisciplinary rehabilitation program. At admission, a thorough clinical assessment was performed. All patients showed the typical PWS clinical phenotype Hass [40]. Cytogenetic analysis was performed in all patients; 11 out of them had interstitial deletion of the proximal long arm of chromosome 15 (del15q11-q13). Uniparental maternal disomy for chromosome 15 (UPD15) was found in one female. All PWS patients showed mild mental retardation. In this respect, one of the requirements for participating in the study was a score over the cut-off value of 24 in the Mini Mental State Examination (MMSE) Italian version [41]. Scores over the MMSE cut-off are recognized as suggesting the absence of widespread acquired cognitive disorders in adult people. Our PWS patients were all able to understand and complete the testing.

Two different reference groups of subjects were specifically recruited for this study and served as controls. The first group included 20 obese patients (Obese Group: OG; 13 females, 7 males; age: 40.7 ± 11.7 years; height: 1.67 ± 0.1 m; BMI: 41.9 ± 4.0 kg/m^2). This group was selected in order to have a BMI match group. Exclusion criteria were the presence of neurological disorders, oculo-vestibular disorders, major musculo-skeletal condition (complicated back, hip and knee pain, flat

foot), hip and knee replacements, and arrhythmia. Inclusion criteria was the ability to walk independently without aids.

The second group consisted of 19 age-matched healthy subjects (Healthy Group: HG; 11 females, 8 males; age: 33.9 ± 11.2 years; height: 1.72 ± 0.1 m; BMI: 21.2 ± 1.3 kg/m^2) recruited among the hospital staff. Inclusion criteria for the HG were no cardiovascular, neurological or musculoskeletal disorders. They had normal flexibility and muscle strength and no obvious gait abnormalities. All participants had normal values in the main laboratory tests, including adrenal and thyroid function. All participants were able to walk independently without aids. The study was approved by the Ethics Committee of the Institute; written informed consent was obtained by the patients.

Experimental setup

The study was performed in the motion analysis laboratory of S Giuseppe Hospital, which is equipped with a 8-m-long walkway and 2 force platforms (Kistler, Winterthur, Switzerland) in order to measure the trajectory of CoP. In this study, only one force platform was used.

For the GI task, subjects were asked to stand barefoot in a relaxed posture, on a bipedal standing position on the force platform with feet in a fixed and parallel position (the distance between their heels was fixed to the pelvis width). Acquisition of force platform data was triggered just prior to the participants receiving a verbal cue to begin walking- approximately 3 s before starting task. In response to the cue, the participants initiated walking; the leading limb stepped off the force platform first, followed by the trailing limb and continued walking for several steps. All the requests were standardized: 3 trials starting with the left foot and 3 trials starting with the right foot. For each subject the gait velocity was self-selected [26, 27].

For the GT task, subjects were asked to walk at their self-selected velocity, to stop walking on the force platform with both legs and to stand still for at least 3 s. The participants terminate walking by stepping with the leading limb on the force plate, followed by placing the trailing limb next to the leading limb. They performed at least three steps prior to the GT step, to achieve the steady-state gait [25]. Adjustment of the step length in order to hit the force plate was avoided by practicing the task in advance to select an appropriate distance from the starting point to the force plate. The subjects were instructed to look at the end of the walkway instead of at the force plate. All the requests were standardized: 3 trials stopping with the left foot and 3 with the right foot. Experimental sessions took place at the beginning of the rehabilitation program for all subjects.

Data analysis

The raw CoP data sampled at a frequency of 1 kHz and low-pass-filtered at 20 Hz was analysed using a dedicate protocol developed using SmartAnalyzer software (version: 1.10.451.0; BTS, Italy).

For each acquisition of GI task, five points were manually identified as shown in Fig. 1a:

1. Origin (initial CoP position)
2. First minimum (1 min): minimum posterior position of the CoP on the leg in swing side
3. First maximum (1max): Maximum anterior position during the CoP transition from the leg in swing to the leg in stance
4. Second minimum (2 min) minimum posterior position of the CoP on the leg in stance side.
5. End (Final CoP position).

For the timing analysis, we divided the task in two phases [7, 24, 27] as shown in Fig. 1b:

1) postural phase, which is computed between a quite standing position and the start of the task. This first phase of GI - typically referred to as an anticipatory postural adjustment (APA). It can be divided into two sub-phases:
   - APA1 begins at the onset of the movement and ends at the release of swing foot vertical loading - this APA is between the origin and the first minimum. It represents the translation of the CoP in lateral and posterior directions together toward the swing foot heel
   - APA2 that begins at swing foot release, ends at the swing toe off, and represents a lateral CoP shift toward the stance foot [7]. APA2 was further divided into two additional sub-phases: APA2a and APA2b defined respectively the anticipatory movement between the first minimum and the first maximum and the anticipatory movement between the first maximum and the second minimum
2) locomotor phase - following referred to as LOC - which is between the second minimum and the end of the COP trajectory.

For each acquisition of GT task, five points were manually identified - as shown in Fig. 2a:

1. Origin (initial CoP position)
2. First maximum (1max): maximum anterior position of the CoP on the leg in swing side
3. First minimum (1 min): minimum posterior position during the CoP transition from the leg in swing to the leg in stance

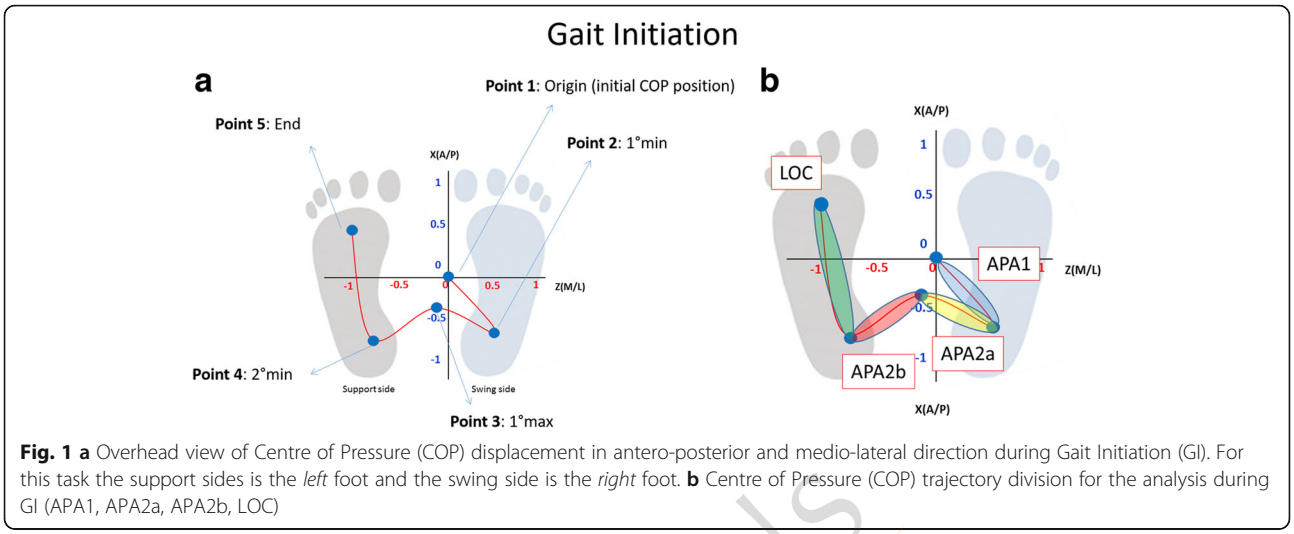

Fig. 1 a Overhead view of Centre of Pressure (COP) displacement in antero-posterior and medio-lateral direction during Gait Initiation (GI). For this task the support sides is the *left* foot and the swing side is the *right* foot. **b** Centre of Pressure (COP) trajectory division for the analysis during GI (APA1, APA2a, APA2b, LOC)

4. Second maximum (2max) maximum anterior position of the CoP on the leg in stance side.
5. End (Final CoP position).

For the timing analysis, we divided the GT task in two phases [1, 25] - as shown in Fig. 2b:

1) locomotor phase - following referred to as SPS 1 (Stopping Postural Adjustment - SPA) - which is between the initial CoP origin to the first maximum of the CoP trajectory
2) postural phase, which is computed between the end of the locomotor phase and the quite standing position.

This phase can be divided into two sub-phases - Fig. 2b:

– SPA 2 that begins at the end of the LOC phase and ends just prior the initial contact of the swing limb. SPA 2 was further divided into two additional sub-phases: SPA 2b and SPA 2a defined respectively the anticipatory movement between the first maximum and the minimum and the anticipatory movement between the minimum and the second maximum
– SPA3 begins at the initial contact of the swing limb and ends at the final bipedal stance position-this phase is between the second maximum and the final CoP position.

According to these phases subdivision, the following parameters have been calculated for both tasks:

- Track duration (s) during each segment (as for GI: TAPA1, TAPA2A, TAPA2B, TOLOC; as for GT: TSPA1, TSPA2A, TSPA2B, TSPA3), and the total duration of the task (TTOT as for GI and GT) (expressed as the sum of the duration of each segment);

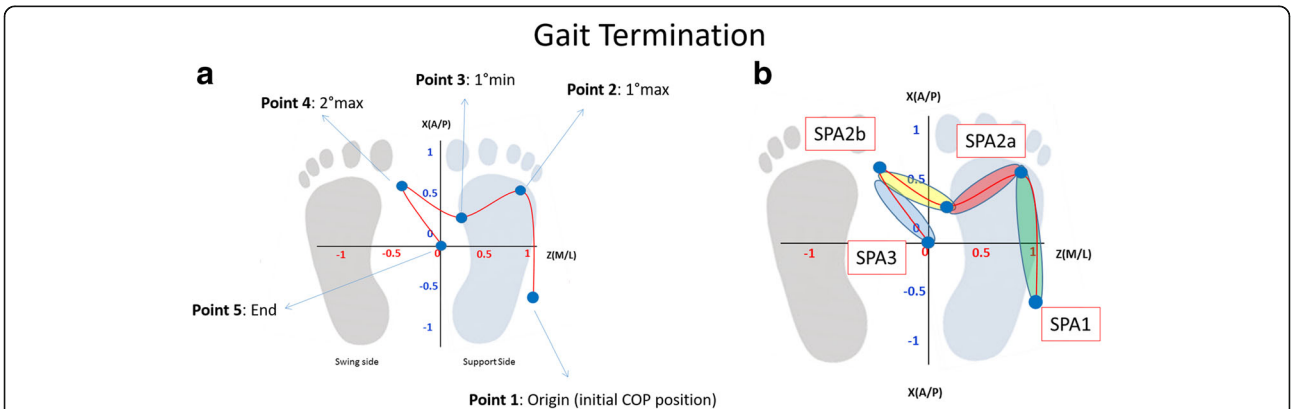

Fig. 2 a Overhead view of Centre of Pressure (COP) displacement in antero-posterior and medio-lateral direction during Gait Termination (GT). For this task the support sides is the *right* foot and the swing side is the *left* foot (**b**) Centre of Pressure (COP) trajectory division for the analysis during GT (SPA1, SPA2a, SPA2b, SPA3)

- Track velocity (m/s) in the segments and in the anterior-posterior direction (x) and in medio lateral direction (z) (as for GI: VAPA1 (x,z), VAPA2A (x, z), VAPA2B (x, z), VLOC (x, z); as for GT: VSPA 3(x,z), VSPA 2a(x,z), VSPA 2b(x,z), VSPA 1(x,z));
- Track length (mm/m) of each segment (as for GI: LAPA1, LAPA2A, LAPA2B, LLOC; as for GT: LSPA3, LSPA2a, LSPA2b, LSPA1) [29]. All track length parameters were normalized by subjects' height (m).

Statistical analysis was conducted using Statistica (version 7.0; StatSoft Inc, USA). All parameters were computed bilaterally for each participant and the median and quartile range values of all indexes were calculated for each group (PWS, OG and HG). Kolmogorov-Smirnov tests were used to verify if the parameters were normally distributed; the parameters were not normally distributed, so we used the Kruskal-Wallis tests followed the post hoc analysis for comparing data among all three groups. Level of significance was set at $p < 0.05$.

Results

Gait initiation

In the starting posture, no differences were found as for feet position in all of the evaluated subjects; we therefore pooled the data from both sides. The values (median and quartile range) of parameters related to GI are displayed in Table 1 for all the evaluated groups. All time durations (TAPA1, TAPA2A, TAPA2B, TLOC and TTOT parameters) were higher in the PWS and OG than HG. The PWS and OG showed lower values of velocities than HG in the anterior/posterior direction (VAPA1x, VAP2Ax, VAP2Bx and VLOCx); in addition, VAPA1x, VAP2Ax and VLOCx were statistically different between PWS and OG, with PWS showing lower values than OG. The velocities in the medial/lateral direction during the APA1 (VAPA1z index) and APA2A phase (VAPA2z index) were statistically lower in PWS with respect to the OG and HG. No statistically differences were displayed in VAP2Bz and VLOCz parameters among the three evaluated groups. The PWS showed statistically lower values than OG and HG of some track lengths (LAPA1, LLOC and LTOT parameters). The LAPA2A length was lower in PWS than OG, but not with respect to HG: PWS showed in fact similar values compared to HG. No differences among groups were found in LAPA2B length.

Gait termination

In the final posture, no differences were found in feet position in all of the evaluated subjects; we therefore pooled the data from both sides. The values (median and quartile range) of parameters related to GT are displayed in Table 2 for all the evaluated groups. The PWS and OG showed higher values than HG of some duration parameters (TSPA3, TSPA2A and TTOT indexes); in addition, TSPA3 was higher in PWS in comparison to OG. As for the velocities, PWS were characterised by lower values of VSPA1x, VSPA3z and VSPA2Az if compared to HG and OG, with the exclusion of VSPA1x, which was similar between PWS and OG. Regarding length parameters, no differences were found between PWS and OG with in general similar values respect to HG. The LSPA2A value was higher in PWS and OG if compared to HG.

A representative figure of the postural sway during both tasks and between the three groups is showed in Fig. 3.

Table 1 Values of median and quartile range for the calculated parameters during Gait Initiation task

GAIT INITIATION	PWS	OG	HG
DURATION [s]			
TAPA1	0.45 (0.21)*	0.44 (0.19) *	0.32 (0.14)
TAPA2A	0.18 (0.08)*	0.17 (0.07) *	0.13 (0.08)
TAPA2B	0.13 (0.06)*	0.13 (0.06)*	0.11 (0.06)
TLOC	0.54 (0.11)*	0.56 (0.11) *	0.50 (0.08)
TTOT	1.34 (0.33)*	1.35 (0.27)*	1.09 (0.23)
VELOCITY [m/s]			
$VAPA1_{(x)}$	0.05 (0.04)*+	0.08 (0.07)*	0.15 (0.12)
$VAPA2A_{(x)}$	0.07 (0.07)*+	0.10 (0.08)*	0.14 (0.10)
$VAPA2B_{(x)}$	0.09 (0.08)*	0.12 (0.10)*	0.18 (0.11)
$VLOC_{(x)}$	0.22 (0.06)*+	0.24 (0.10)*	0.29 (0.10)
$VAPA1_{(z)}$	0.05 (0.05)*+	0.09 (0.07)	0.08 (0.08)
$VAPA2A_{(z)}$	0.29 (0.18)*+	0.39 (0.26)	0.39 (0.24)
$VAPA2B_{(z)}$	0.35 (0.23)	0.42 (0.20)	0.39 (0.23)
$VLOC_{(z)}$	0.03 (0.05)	0.03 (0.03)	0.02 (0.03)
LENGTH [mm/m]			
LAPA1	0.029 (0.010)*+	0.041 (0.019)	0.040 (0.019)
LAPA2A	0.037 (0.018)+	0.052 (0.029) *	0.035 (0.019)
LAPA2B	0.036 (0.018)	0.032 (0.026)	0.028 0.025)
LLOC	0.080 (0.011)*+	0.093 (0.023)	0.092 (0.016)
LTOT	0.180 (0.035)*+	0.216 (0.052)*	0.192 (0.039)

PWS (Prader-Willi Syndrome group), OG (Obese Group) and HG (Healthy Group). * = $p < 0.05$, PWS and/or OG Vs. HG;, + = $p < 0.05$, PWS Vs. OG

Discussion

GI, the transition from standing to walking, and GT, from walking to standing, may represent destabilizing activities for PWS patients. In this study, we aimed to quantitatively compare the GI and GT patterns of adult PWS individuals with those observed in non-genetically obese and in lean individuals. Due to the common occurrence of mental retardation, however, it could be argued that cognitive impairment may have a significant

Table 2 Values of median and quartile range for the calculated parameters during Gait Termination

GAIT TERMINATION	PWS	OG	HG
DURATION [s]			
TSPA1	0.40 (0.08)	0.46 (0.13)	0.43 (0.11)
TSPA2A	0.19 (0.16)*	0.19 (0.15)*	0.14 (0.09)
TSPA2B	0.17 (0.10)	0.13 (0.11)	0.15 (0.13)
TSPA3	0.55 (0.12)*+	0.50 (0.22)*	0.39 (0.05)
TTOT	1.37 (0.25)*	1.29 (0.40)*	1.12 (0.23)
VELOCITY [m/s]			
VSPA $1_{(x)}$	0.26 (0.15)*	0.29 (0.12)*	0.37 (0.12)
$VSPA2A_{(x)}$	0.06 (0.07)	0.07 (0.07)	0.07 (0.09)
$VSPA2B_{(x)}$	0.08 (0.07)	0.06 (0.09)	0.10 (0.07)
$VSPA3_{(x)}$	0.03 (0.04)	0.03 (0.04)	0.03 (0.03)
VSPA1 $_{(z)}$	0.05 (0.09)	0.06 (0.09)	0.05 (0.09)
$VSPA2A_{(z)}$	0.19 (0.15)*+	0.27 (0.23)	0.25 (0.25)
$VSPA2B_{(z)}$	0.33 (0.21)	0.33 (0.38)	0.27 (0.21)
$VSPA3_{(z)}$	0.02 (0.03)*+	0.04 (0.05)	0.04 (0.06)
LENGHT [mm/m]			
LSPA1	0.083 (0.038)	0.088 (0.033)	0.095 (0.033)
LSPA2A	0.031 (0.018)*	0.029 (0.031)*	0.025 (0.023)
LSPA2B	0.034 (0.013)	0.032 (0.029)	0.030 (0.017)
LSPA3	0.025 (0.019)	0.028 (0.019)*	0.022 (0.014)
LTOT	0.175 (0.068)	0.180 (0.053)	0.175 (0.034)

PWS (Prader-Willi Syndrome group), OG (Obese Group) and HG (Healthy Group). * = $p < 0.05$, PWS and/or OG Vs. HG;, + = $p < 0.05$, PWS Vs. OG

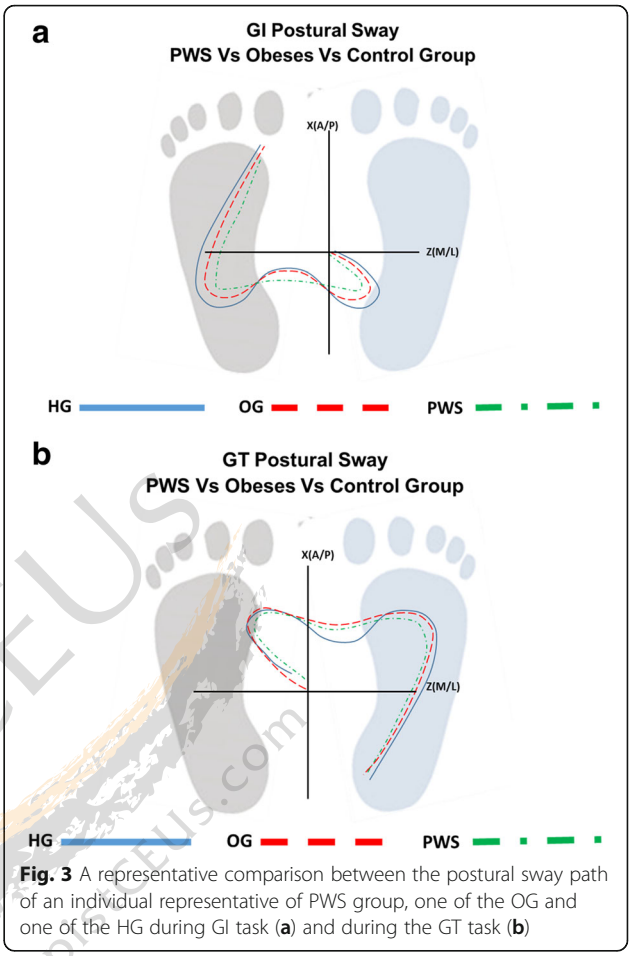

Fig. 3 A representative comparison between the postural sway path of an individual representative of PWS group, one of the OG and one of the HG during GI task (**a**) and during the GT task (**b**)

influence on the values observed in PWS. Nevertheless, the inclusion criterion of a score >24 in the MMSE, a reliable method to rule out a serious deterioration of mental functions, seems to exclude this negative effect.

As for GI, the results showed a significant reduction of velocity and CoP length parameters in PWS, with respect to the non-genetically obese subjects. The excessive body weight of the PWS leads, together with a reduced muscle strength and motor control, characteristic features of these individuals [32, 42], to a further reduction of the velocity and length parameters during most of APAs phases, as compared to OG and HG [27]. The role of the adductor hip muscles is fundamental for GI; in fact, these muscles allow the shifting of CoP from one side to the contralateral [26]. The results obtained in this study could be related to a reduction of hip adductor activity in the PWS patients. Short feet and height, which are common features of PWS patients, may have also accounted for the reduction in CoP length. However, to exclude it, the CoP length parameters were presented after normalization to the patients' height. As lower normalized values were observed in PWS, we can speculate that reduced muscle strength and motor control in PWS as compared to the non-genetically obese population may have had a significant impact on reduction in CoP length.

Longer durations, similar to OG, were observed in PWS than HG during GT. Velocity is reduced when compared to OG and HG, especially in medial-lateral direction and in the terminal part of GT (SPA2A and SPA3). We can speculate that this strategy may be used by PWS patients in order to achieve better stability while terminating gait. These results could be related not only to the excessive body mass but also to the decreased motor control of PWS [37]. It appears therefore likely that they use a more cautious strategy and a slower pace at the end of GT.

From our experimental data, GI appears to be a demanding task in most of its sub-phases (APA1, APA2A and LOC) for PWS individuals, while GT seems to require caution only towards the end of the task. It appears even more so that the combination of high body mass, reduced motor control and muscle strength could account for PWS difficulties in negotiating GI. The difference in the results could be related to the more complexity of GI. In GI APAs contribute to postural stability

and to create the propulsive forces necessary to reach steady state gait at a predefined velocity and may be indicative of the effectiveness of the feedforward control of gait. Our findings could be related to an abnormal muscular activation pattern mainly characterized by a disruption of the synergistic activity of antagonistic pairs of postural muscles and they suggest that individuals with PWS might lack accurate tuning of feedforward control of movements at GI. In addition, the practice of the task for GT could influence this difference.

Conclusions

Possible rehabilitative spin-offs of this study include the implementation within the rehabilitation program of specific exercises to improve stability and motor control. In particular, breaking the cycle of gait into the phases of GI and GT and implementing specific exercises focusing on weight transfer and foot clearance during the transition phase from the steady condition to gait will possibly improve the effectiveness of rehabilitation and fall and injury prevention. In addition, balance exercises, eye/feet coordination, walking on different surfaces and crossing obstacles are some of the goals in motor rehabilitation.

The limitations of this study were the followings: firstly, only data related to CoP trajectory were investigated while no evaluations of lower limb joints kinematics and kinetics were conducted. As it represents the first attempt to quantify GI and GT strategies of individuals with PWS, we decided to perform the assessment using only one force platform, with a less time-consuming evaluation than a thorough 3D investigation including markers placement. Secondly, the small number of participants resulting in limited strength of the statistical findings. We have to bear in mind, however, that PWS is a rare genetic condition and large experimental samples are difficult to gather. However, it is important to underline that, despite these limitations, this represents the first study focusing on GI and GT performance in PWS subjects.

Physiological adaptation after a 12-week physical activity program for patients with Prader–Willi syndrome: two case reports

Abstract

Background: Physical activity programs are a powerful tool against several diseases including obesity and their comorbidities. Prader–Willi syndrome is the most common genetic disease associated with obesity, and brings with it behavioral and emotional problems that need complex management. Research into the effect of physical activity programs on Prader–Willi syndrome is limited and it is frequently argued that if a physical activity program is too complex, the participants are more likely to drop out. Therefore, in this study, we assessed the physiological adaptation effect of a physical activity program with increasing complexity and load, in a boy and a girl with Prader–Willi syndrome by assessing changes in lipid profile, body composition, and physical fitness parameters.

Case presentation: Case 1 was an 11-year-old girl, mixed race (brown), with an intelligence quotient of 68, 52.0 % body fat, and a body mass index of 45.3 kg/m^2. The Prader–Willi syndrome diagnosis was made when she was 5-years old and was found to be due to an imprinting genomic defect. Case 2 was a 14-year-old boy, mixed race (brown), with an intelligence quotient of 74, 48.8 % body fat, and a body mass index of 37.3 kg/m^2. The diagnosis was made when he was 10-years old and was found to be caused by gene deletion. Both participants presented physical characteristics and behavior problems typical of Prader–Willi syndrome. Case 2 presented high blood pressure, high cholesterol and sleep apnea and had to use continuous positive airway pressure to sleep. Both participants were assessed for 12 weeks (three times a week) using a physical activity program designed to improve strength and muscle hypertrophy. The work load was progressively adjusted as necessary and new exercises were added to the program. Prior to the program, the participants' parents received instructions about managing problem behavior and advice about nutrition.

Conclusions: After physical activity program several health markers assessed by biological tests and parental report had improved in both participants. The participants positively accepted the adaptations made to the physical activity program during the study. More studies are necessary to assess the benefits of physical activity in the Prader–Willi syndrome population.

Keywords: Physical activity, Prader–Willi syndrome, Physical fitness and body composition

Background

Prader–Willi syndrome (PWS) is the genetic disorder most frequently associated with obesity. People with PWS do not experience a feeling of satiety, even postprandial, due to hypothalamic abnormality [1]. Endocrine and metabolic alterations such as growth hormone (GH) deficit and gonadotrophic hormone deficit effectively contribute to the development of obesity and metabolic syndrome [2]. PWS is also marked by cognitive difficulties such as intellectual disability and executive function deficits [3]. Ritualistic behavior and explosive outbreaks of anger, particularly when the individual's routine is broken, are common [4, 5]. All these associated conditions contribute to lower levels of physical activity and/or adherence to physical activity programs (PAP) [6]. Among the studies that report the effects of PAPs in PWS, most of them comprise unchanged routines throughout the program [7–10]. It is argued that increasing task complexity and the physical stress caused by the exercise could lead to the participants dropping out of the training programs [11]. However, interventions designed with unchanging activities can limit physiological adaption [12, 13]. Therefore, the present study assessed the physiological adaptation effect of a PAP with increasing complexity and workload in a boy and a girl with PWS by measuring lipid profile, body composition, and physical fitness parameters. This study was approved by the Research Ethics Committee of Mackenzie Presbyterian University (CEP/UPM N° 1432/04/2012).

Assessment and instruments

For cognitive and behavioral characterization, an estimate intelligence quotient (IQ) score was obtained through the Wechsler Intelligence Scale for Children – third edition (WISC-III) subtests Block Design and Vocabulary [14] and the Child Behavior Checklist for ages 6 to 18 (CBCL/6–18) [15]. Anthropometrics data from participants were measured and their body mass indices (BMI) were calculated according to the World Health Organization (WHO) child growth standards [16]. A dual-energy X-ray absorptiometry scan (Discovery Wi – S/N 84206, Hologic Inc.) was used to assess body composition parameters such as percentage of body fat, lean mass, bone mineral density (BMD), and bone mineral content (BMC) of the lumbar spine and body total [17]. A battery of measures and somatomotor tests called PRODOWN were administered to obtain flexibility, strength, explosive strength, agility, displacement velocity, and cardiorespiratory endurance measurements [18]. In addition, daily physical activity was measured using pedometers and a physical activity level questionnaire (PALQ) [9]. Fasting blood analyses was conducted to obtain a lipid, glycemia, and uric acid profile. A complete description of items for each assessment is included in Table 1.

Table 1 Pre- and post-intervention assessment types and their respective instruments

Assessment	Rate/Tool
Wechsler Intelligence Scale for Children – third edition	Subtests Block Design and Vocabulary
Children Behavior Checklist 6–18 years	Questionnaire
Anthropometrics	Weight
	Height
	Body mass index
Body composition	Dual-energy X-ray absorptiometry used for assessing total and lumbar bone mineral density, bone mineral content, body fat rate, and lean mass
PRODOWN battery of measures and somatomotor tests	Flexibility test (sit and reach test)
	Abdominal strength endurance test
	Lower limbs explosive strength test (standing long jump)
	Upper limbs explosive strength test (medicine ball throw)
	Agility test (square test)
	Displacement speed test (20-meter run)
	Cardiorespiratory capacity test (6 minutes)
Physical activity level	Physical activity level questionnaire
	Spontaneous physical activity (pedometer)
Blood parameters	Standard protocols for blood measures (cholesterol, glycemia, triglycerides, and uric acid)

PAP

The PAP was based on tasks successfully used in previous studies on PWS [9, 10]. The complete program was composed of 36 sessions of 60 minutes delivered over 12 weeks (Table 2). Every 3 weeks, a new task was introduced and loads were adjusted. The proposed exercises were: ankle dorsiflexion on platform, hip extension, bench squat, medicine ball chest pass, overhead medicine ball catch and throw, ball games, 40-meter run, and playful activities with ball and balloon.

Case presentation

Case 1

Case 1 was an 11-year-old girl with a cytogenetic diagnosis of PWS due to mutation in the imprinting center. The diagnosis was confirmed when she was 5 years and 8 months old. She presented intellectual disability (IQ=68) and the main behavioral problems reported by her parents were: not being very active, feeling tired without reason, being too dependent, having poor motor coordination, skin picking, not following rules, being stubborn, and screaming a lot. She lived with her father, stepmother, and two older siblings; she was enrolled in the fourth grade of

Table 2 Training program according to phase, duration, and type of training

Phase	Duration	Type of training
1	3 weeks (3 times a week)	Muscular Endurance 1: ankle flexion and extension, throw a 2-kg medicine ball Coordination: keep a balloon suspended by using different body parts and objects Aerobic: 15-minute walk
2	3 weeks (3 times a week)	Muscular Endurance 1: as in phase 1, but with a 3-kg medicine ball Muscular Endurance 2: hip elevation, catch and hold a 2-kg medicine ball as it bounces from the floor Coordination: bounce the ball, throw it up and hold Aerobic: 30-minute walk
3	3 weeks (3 times a week)	Muscular Endurance 1: as in phase 2 Muscular Endurance 2: as in phase 2, but with a 3-kg medicine ball Muscular Endurance 3: stand up and sit on a bench Coordination: bounce a ball with alternate hands, throw up and hold with only one hand Aerobic: 30-minute walk
4	3 weeks (3 times a week)	Muscular Endurance 1: as in phase 3 Muscular Endurance 2: as in phase 3 Muscular Endurance 3: as in phase 3 Muscular Endurance 4: go up and down one step Coordination: bounce a ball with alternate hands, throw up and hold with only one hand, with alternate hand for throw and reception

a mainstream elementary school. She had poor reading and writing skills. Her parents reported that despite their frequent requests for the school to control her food intake no action had been taken and after 5 months she had gained 10 kg.

During the pre-intervention assessment, her parents reported that she was not very active and spent most of the time sitting, watching TV or playing with her dolls. She walked with difficulty when she had to cover longer distances and often stopped to rest.

During the initial assessment, she remained quiet, listening attentively to the orientations for the tasks and demonstrated interest and willingness to start the PAP. Her parents received orientation from a nutritionist trained in PWS who offered menu recommendations adapted to the disorder. They also attended workshops held by a psychologist who gave advice about phenotypic behavioral characteristics and the behavioral management of PWS.

After considering her availability, it was decided to carry out the PAP at our university twice a week and at her house once a week. She accepted positively all the PAP routines, and most of the time the inclusion of new exercises. In the face of new challenges, she understood that they should be overcome. A higher number of repetitions or changing to a heavier medicine ball was also almost always well accepted. If she complained about some change in the PAP, the instructor explained that the alteration was important for her health. She seemed to understand and the session continued. The increase in the number of repetitions was the main cause of complaints. However, the inclusion of games was a motivator to complete tasks. She was praised after completing set tasks to reinforce the behavior. In the final assessment, her parents reported that before the beginning of the PAP she used to have nocturnal enuresis, which ceased after the 12 weeks of training. She attended 95 % of the sessions. Table 3 presents anthropometric and body composition results pre- and post-intervention. There were no initial results for uric acid and glucose for her, but after the PAP they were found to be at normal levels for sex and age (79 and 61.1 mg/dL respectively). In addition, she presented a reduction in total cholesterol (pre=166; post=159 mg/dL), very low-density lipoprotein (VLDL; pre=16; post=14 mg/dL), high-density lipoprotein (HDL; pre=42; post=33 mg/dL), and triglyceride (pre=82; post=72 md/dL), and a small increase in low-density lipoprotein (LDL; pre=109; post=112 mg/dL).

Case 2

Case 2 was a 14-year-old boy with a cytogenetic diagnosis of PWS due to a gene deletion. The cytogenetic test was carried out when he was 10 years and 10 months old. He attended ninth grade elementary school; he had poor writing and reading skills. He had no history of fracture or surgery, but displayed some typical alterations such as myopia. He had minor health problems, such as rhinitis and sinusitis, and other health problems that require special care such as hypercholesterolemia, hypertension, fatty liver disease, and sleep apnea syndrome. He used a continuous positive airway pressure (CPAP) apparatus to facilitate air flow through his upper airway. From the first moment, he demonstrated interest in taking part in the PAP. Such interest was observed in his effort to take the initial assessment tests. He also demonstrated good physical condition and willingness, so that by the third week he was able to perform the complete set of tasks. From the fourth week, three repetitions of 5×40 meters run were added, as well as 5-meter anteroposterior and lateral exercises in a sand box. Whenever he demonstrated being tired or irritable, these exercises were reduced to one repetition. On Saturdays, training sessions took place on a street near his house. It is noteworthy that the street has a 30° angle incline and that the running practice happened in the ascending direction. He sometimes complained during the interval between repetitions; however, he accomplished all tasks after being encouraged. In order to provide new challenges, from the fifth week, a bonus activity was

Table 3 Anthropometric and body composition data

Assessed item	Participants					
	Case 1			Case 2		
	Data		Variation	Data		Variation
	Pre	Post		Pre	Post	
Height (cm)	136.0	138.0	+2.0	151.0	151.0	0
Total body mass (g)	84,056.8	80,733.8	−3323.0	85,168.4	88,147.7	+2979.3
BMI (kg/m^2)	45.3	42.5	−2.8	37.3	38.7	+1.4
Fat mass (g)	43,712.2	40,726.4	−2985.8	41,568.5	45,265.2	+3696.7
Lean mass (g)	39,358.7	38,996.3	−362.4	42,094.1	41,286.9	−807.2
Body fat (%)	52.0	50.4	−1.6	48.8	51.4	+2.6
Total BMC (g)	985.9	1011.1	+25.2	1505.8	1595.5	+89.7
Total BMD (g/cm^2)	0.874	0.877	+0.003	0.873	0.908	+0.035
Total z-score	0.0	−0.2	−0.2	−2.1	−1.7	+0.4
Spinal BMC (g)	24.79	25.30	+0.51	32.71	32.88	+0.17
Spinal BMD (g/cm^2)	0.671	0.714	+0.043	0.747	0.757	+0.010
Spinal z-score	−0.3	−0.1	+0.2	−0.8	−0.9	−0.1

BMC bone mineral content, *BMD* Bone mineral density, *BMI* body mass index

implemented. The activity consisted of a continuous run with increasing distance every week; it started with 60 meters and reached 200 meters in the last week. He also attended 95 % of the sessions.

A positive aspect of the PAP was the participants' willingness to perform tasks and their frequent request to continue them. This fact can be associated with the introduction of playful elements and the constant encouragement offered during the program. Table 3 presents anthropometric and body composition results pre- and post-intervention. Case 2's blood test results after the PAP presented an improvement in important health indicators, reaching health-related values for sex and age for uric acid (pre=7.2; post=5.5 mg/dL), total cholesterol (pre=235; post=182 mg/dL), LDL (pre=153; post=119 mg/dL), VLDL (pre=29; post=19 mg/dL), and triglyceride (pre=143; post=95 mg/dL). An increase in glucose (pre=87; post=115 mg/dL) and a reduction in HDL (pre=53; post=44 mg/dL) were also observed.

Table 4 describes the results of PRODOWN physical fitness assessment tests and level of daily physical activity (pedometer and PALQ). Both participants improved their performance in the post-intervention test of upper limb muscle power, agility and 20-meter displacement speed. The female participant (Case 1) demonstrated an improvement in the lower limb power test. The male participant (Case 2) also presented an improved level of physical activity, with a higher number of steps and distance covered, as

Table 4 PRODOWN physical fitness and Level of Daily Physical Activity test results

Protocol/Assessed item		Participants					
		Case 1			Case 2		
		Assessment		Variation	Assessment		Variation
		Pre	Post		Pre	Post	
PRODOWN physical fitness	Flexibility sit and reach (cm)	27	27	0	0	2	+2
	Abdominal endurance	0	0	0	0	0	0
	Lower muscles power (cm)	10	24.2	+14.2	76	63	−13
	Upper muscles power (cm)	177	200	+23	275	310	+35
	Square agility (seconds)	15:25	13:39	−1:86	9:30	9:20	−0:10
	20-m displacement speed (seconds)	11:56	11:03	−0:53	6:60	6:30	−0:30
	6-minute run (m)	400	395	−5	580	507	−73
Pedometer	Steps	15,423	10,825	−4595	24,529	31,345	+6816
	Distance (m)	6939	5414	−1525	15,942	20,374	+2865
PALQ	Score	211	199	−12	231	310	+79

Sum of 3 days. Daily recommendation >10,000 steps. *PALQ* physical activity level questionnaire

well as an increase in PALQ total score. For the 6-minute run test, there was little variation for the female participant and a reduction in performance for the male participant.

Discussion

The participants presented characteristic PWS phenotypic features [19] and both had late cytogenetic diagnosis and were not taking recombinant human growth hormone (rhGH). This might be responsible for both participants presenting such high levels of body fat (~50 %) and short stature at baseline.

During the 12 weeks of the PAP, the female participant grew in height while losing body mass (90 % consisted of fat mass). This result is similar to other studies and demonstrates the positive effect of physical activity for the reduction of body fat [9, 10]. In contrast, the male participant had an increase in body mass, mainly because of an increase in body fat. The lack of supervision of his food intake seems likely to be the main reason for the increase in body fat. Regarding bone status, an increase was observed in lumbar BMD for the female participant and total body BMD for the male participant after the PAP. Before the program, the male participant presented low total body BMD (z-score is −2.1) and after the PAP, the value achieved normal range (z-score is −1.7). According to Duran and colleagues [20], there is a positive correlation between higher levels of physical activity and bone density in PWS. It is possible that the increased physical activity due to PAP contributed to the improvement of the BMD in both participants.

Unlike nonsyndromic obesity, overweight in PWS is not accompanied by an increase in lean mass. Low lean mass and high fat mass could contribute to low levels of physical activity in PWS. In the present study, the female participant displayed a low level of physical activity as assessed by steps/day and questionnaire, while the male participant had a moderate level. Even with a reduction in the level of daily activity measured by the pedometer, the physical educator who implemented the PAP perceived that she improved her willingness and readiness for the accomplishment of daily activities, and was less fatigued during walking. In contrast, the male participant showed an increased level of physical activity, reaching healthy values of over 30,000 steps/day.

In the PRODOWN test, both participants presented improved results for almost all measured variables. However, in the 6-minute test, both participants presented less distance covered after the PAP compared to the initial assessment. Similarly, the male participant did not improve lower limb power. When considering the reasons as to why no improvements were observed in the 6-minute test, it is possible to consider that the participants did not provide their maximum effort. Although the female participant's data in blood analysis is fragmented, it was possible to observe positive changes in her cholesterolemic profile. This result is consonant with current literature concerning the effects of physical activity on an individual's blood profile. Although the male participant had an increase in body fat rate, his blood markers indicated an improvement in indexes related to coronary diseases such as LDL, VLDL, triglyceride, and total cholesterol. Their body weight was checked every week and fluctuations during the PAP were observed. In the case of the male participant, such variations may be related to his parents' difficulties in controlling his access to food.

Energy balance management is the most important task and the highest concern among physicians and parents in the PWS population. Beside the control of energy intake, introducing physical activity into the daily routine is the best non-pharmacologic strategy to maintain healthy weight and prevent obesity. Although patients with PWS are acknowledged to have behavior problems caused by breaks to routines, in this case report the introduction of PAP and the additions made to it over the period of the study did not affect the participants' moods, even during strenuous exercises. This study was the first to report the effect of PAP on the behavior of patients with PWS. Future studies with a larger sample should investigate how physical activity may affect behavior in patients with PWS.

The key limitations of this study were the small number of participants and the relatively short period of implementation of the program. A longer program would be necessary for the effects of physical activity to be more evident.

Introducing PAP was challenging due to the complexity of PWS. Constant adaptations were required to meet the participants' needs and the dynamics of each family. As reported in the current literature and observed here, interdisciplinary actions are essential for the success of intervention practices in PWS [10, 21]. This study observed that parental support from psychology, psychiatry and nutrition professionals was essential for the PAP to succeed.

Conclusions

The completion of this PAP resulted in positive effects in both participants with PWS. Several physical fitness indicators improved, such as body fat reduction, agility, and upper/lower muscle power for the female participant, increased spontaneous physical activity for the male participant and an improvement in upper muscle power. Both participants showed improvement in blood health parameters as well as in bone density. Despite the PAP being successful in improving fitness and health parameters without causing behavioral problems, there is need for constant and multi-professional family support as provided in this intervention.