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Specific treatment of Prader–Willi syndrome through cyclical rehabilitation programmes

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Abstract

Purpose. To evaluate retrospectively the efficiency of our rehabilitation programme for patients with Prader–Willi Syndrome. In total, 49 patients were examined, 21 female and 28 male, the youngest in their late teens. Prader–Willi syndrome is generally characterised by cognitive impairment, behavioural abnormalities, and hyperphagia. Patients are usually considerably adverse to any form of physical exercise, and despite hormonal therapy, weight control in adult patients can be difficult.

Methods. Four times a year, disease-specific residential programmes were organised, each lasting 4 weeks. The patients were restricted to a 1500 Kcal diet. In addition, they were required to do 6.5 h of physical exercise daily, stamina being built up by using music therapy, psychomotor therapy, education and entertainment activities.

Results. BMI decreased by 2.1 average points in every residential session. For three patients who attended our treatments regularly, a reduction of 8.9 points over 6 years was recorded. An attendance of at least three sessions per year seemed to be necessary to substantially reduce weight.

Conclusions. A multidisciplinary approach and a daily calorie-counted diet can lead to significant weight loss in teenage and adult PWS patients. This approach would also be suitable in treating patients with other obesity syndromes with mental retardation.

Keywords: *Prader–Willi syndrome, psychomotor therapy, music therapy, weight loss, compulsive behaviour*

Introduction

Prader–Willi Syndrome (PWS), the most common genetic obesity syndrome, is a rare inborn genetic disorder (prevalence of 1:10,000–1:25,000). The absence of any paternal contribution to chromosome region 15q11-q13 is mainly due to a hemizygous deletion or uniparental disomy (UPD) [1]. From an endocrinological standpoint, PWS shows a typical hypothalamic-pituitary dysfunction [2], characterised in particular by hypogonadism and low growth hormone (GH) levels throughout life. Patients affected by Prader–Willi Syndrome (PWS) are 'floppy infants' at birth with hypotonia, and failure to thrive. The reduced muscle tone will remain one of the hallmarks of the disease, even if it usually improves at about 8–10 months after birth. At 1–6 years of age an uncontrolled hyperphagia appears, rapidly leading to obesity, if not restrained. Glucose metabolism is frequently impaired, and oral antidiabetics are often administered [3]. Human growth hormone (HGH) replacement therapies are commonly used to correct the growth deficiency [4], despite some isolated emerging concerns about adverse long-term effects in children [5]. HGH has now also proved to play an important role in adulthood, helping to improve the fat/lean body mass ratio and exercise capacity [6,7].

However, despite HGH treatment in PWS patients, mental retardation, behavioural abnormalities

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and compulsive hyperphagia impede patients' social acceptance and development [8]. Unrestrained hyperphagia very often leads to severe obesity and a vicious cycle sets in: obesity results in sleep apnoea, subsequent drowsiness during daytime hours [9] and hence less activity and weight increase. It should also be noted that PWS patients are difficult to care for at home because of their obsessive-compulsive traits, such as temper tantrums and skin picking [10–11]. This frequently leads to treatment with antipsychotic drugs, which eventually contribute to the aforementioned loop. From infancy onwards, when hyperphagia appears, patient care focuses mainly on weight control, thus also preventing the onset of secondary diseases, and improving self-sufficiency, and social integration [12–13].

Much has been published on the management and weight control of PWS patients during childhood and adolescence [14]. On the contrary, little has been reported on the management of adult PWS patients [15]. Difficulties in the daily care of PWS patients and their weight control have been highlighted by Van Hooren et al. [16]. PWS patients in their 30s and 40s are reported, by Dykens E.M., to be at highest risk of maladaptive and compulsive behaviour [17].

The multidisciplinary approach we are proposing focuses on this second age group: the older teenager and adult PWS population. However, the recent dramatic increase in life expectancy of PWS patients forces us to re-evaluate current patient management [18].

Moreover, the use of multiple and prolonged treatments per year gives families a much needed break. The average BMI improvement obtained by our approach, of 2.1 points at every cycle in the last 2 years' PWRs, is the result of a 6 years-experience. Many unanswered questions arose from our study, which we are now trying to address.

Patients and methods

PWS subjects

Among the PWS subjects who visited our institution for evaluation, 53 (28 males and 25 females) decided to undergo our Prader–Willi specific rehabilitation treatment cycles (PWRs). The patient's genotype was recorded, and a physical examination and psychiatric evaluation performed. If not available, genetic analysis was carried out in the genetic lab of our institute.

After working with the first few cases, some involving quite young patients, we focused our attention on 49 teenager and adult patients (28 males and 21 females). The average lifetime of the treated population was 25.12 years (SEM 0.99) and the patient age distribution ranged between 13 and 42 years. All PWS patients were genetically characterised. Thirty-three (16 females, 17 males) showed a deletion in the paternal chromosome region 15q11.2-q13; 6 (1 female, 5 males) had maternal UPD of chromosome 15, and 10 (5 females, 5 males) were positive to the methylation test and negative for the 15q11.2-q13 deletion (UPD test could not be performed). A summary of the patients involved in the study is reported in Table I. The PWRs were organised regardless of the genotype and disability severity.

The study was performed after approval by the institutional ethics committee and written consent was obtained, under parental guidance, from PWS patients.

Patients parameters recorded on admission /discharge

The core of our multidisciplinary PWS rehabilitation team is composed of a psychiatrist, a rehabilitation physician, a geneticist, and a neurologist. In addition, a psychologist, a music-therapist, two therapists for neuro- and psychomotricity, a physiotherapist, a dietician, and two supervisors complete our team.

On admission, the physical examination included measurements of height, weight, and body mass index (BMI) (calculated as weight in kilograms divided by the square of height in centimetres). Psychiatric evaluation was performed by interview in order to assess the clinical features, and to delineate the endpoints of our treatment. The drug schedule was evaluated and temporarily modified during the PWR if necessary. On discharge a final report was given to every patient. It included a physical and psychiatric final evaluation, with special focus on the patient's achievements, drug therapy schedule on dismissal, and advice for further medical examinations.

Rehabilitation: frequency, duration, and daily schedule of the treatment cycle

Before 2006, PWRs duration was 2–3 weeks, and frequency varied widely. At first, PWRs were open to patients of all ages. After the second PWR, the youngest of patients were discouraged to participate, and the PWRs were in fact restricted to teenage and adult patients. Therefore, early teen PWS data are not included in the present study. Since 2006, the PWRs duration has been of 4 weeks – exactly 26 days – with a frequency of 4 PWRs/year. Patients are admitted to the institute on Monday morning of the first week, and are discharged on Friday afternoon of the last week. Because PWS patients usually display

Table I. PWS patients.

Patient n°	Sex	Age on admission	Age at discharge	BMI on first admission	BMI on final discharge	Attendance (cycles)
1	M	13	18	28,04	25,16	20
2	F	26	30	51,6	55,6	6
3	F	22	22	32,56	30,96	2
4	F	26	26	20,67	20,42	1
5	M	23	27	49,24	48,22	6
6	M	16	17	23,39	24,96	2
7	M	42	42	47,59	44,6	1
8	M	31	32	50,59	43	4
9	F	35	35	51,73	50,8	1
10	M	30	32	41,02	39,92	2
11	M	14	14	39,3	38,49	1
12	F	14	14	35,63	34,71	1
13	F	39	39	30,31	29,8	1
14	M	25	25	41,88	41,88	2
15	F	30	33	33,55	26,65	13
16	F	21	25	45,13	29,64	20
17	M	26	30	31,84	35,34	3
18	M	29	32	38,67	39,78	2
19	F	27	27	53,05	48,42	1
20	F	15	16	51,53	53,45	2
21	F	13	17	32,86	28,12	5
22	M	16	17	27,64	28,05	2
23	M	20	24	31,03	22,19	8
24	M	16	16	23,73	23,43	1
25	F	35	36	41,09	37,16	2
26	M	17	20	21,73	22,27	8
27	M	28	28	50,11	49,2	1
28	M	16	20	33,31	38,88	2
29	M	22	23	44,7	40,34	5
30	M	17	17	46,18	44,43	1
31	M	24	25	29,73	22,85	4
32	F	15	16	31,84	31,22	1
33	F	31	32	24,38	27,3	6
34	M	33	33	29,34	25,29	2
35	F	20	21	37,12	33,01	2
36	M	16	16	28,5	27,11	1
37	M	19	20	33,83	30,78	3
38	M	18	19	49,13	45,04	5
39	F	26	26	48,22	46,44	1
40	M	32	32	36,09	34,73	1
41	M	26	26	29,6	28,84	1
42	F	26	27	48,39	40,94	3
43	F	32	33	47,44	40	3
44	F	24	29	46,09	41,05	3
45	M	27	31	41,18	32,49	6
46	M	19	20	58,69	42,79	2
47	M	21	22	34,63	33,72	1
48	F	22	22	53,07	51,76	1
49	F	27	27	39,01	38,5	1
	M=28 - F=21	**23,7 (±1,0)**	**25,1 (±0,9)**	**38,7 (±1,4)**	**36,1 (±1,3)**	**3,5 (±0,6)**

Characteristics of the PWS population that attended the rehabilitation cycles.

poor social abilities, group treatments are the preferred option.

A crucial aspect of PWR is weight control through physical exercise [14,19]. A physical training consisting of exercises was performed daily, except on Sunday (see Table II). Calories consumption during exercise was calculated comparing data from the USDA (United States Department of Agriculture) chart and from the site of the official journal of the American College of Sports Medicine: Medicine & Science in Sports & Exercise. Morning exercises consisted of 30 min on a stationary bike (theoretical calories expenditure, on average: 800 Kcal/h), followed by 30 min of step activity (theoretical calories expenditure, on average: 500 Kcal/h) and 60 min of exercise on the exercise mat (theoretical

Table II. Daily exercise schedule.

Daily schedule	Time	Theoretical calorie expenditure (Kcal/h)
Morning		
Exercise bike	30 min	800
Step activity	30 min	500
Exercise mat	60 min	500
Walking	90 min	500
Afternoon		
Walking	90 min	500
Psychomotor and music therapy	(120 min)	
Walking	90 min	500
Total	**6h 30' (+2h)**	**3300**

The daily activity schedule is summarized. On the right hand column, the theoretical calories burnt are reported, but – due to the experimental conditions that prevailed – it is difficult to deduce what the real figure is. On the contrary, the calories burnt in 2 h of psychomotor or music therapy is unpredictable, because motor exercise associated to these activities vary broadly.

calories expenditure, on average: 500 Kcal/h). These activities were performed slowly, resulting in much lower energy expenditure. Every workout was followed by an appropriate period of rest. The morning workout was completed with 90 min of walking, outdoors, weather permitting, otherwise indoors (calorie expenditure, on average: 500 Kcal/h).

In the afternoon, patients were asked to walk for two sessions, 90 min per session. Two hours of psychomotor and/or music therapy and recreational activities were inserted in between these walks. The total time spent exercising was 6.5 h a day, with an additional 90 min of recreational activities.

This daily exercise schedule was in some cases lightened for patients with less severe BMI conditions.

On Sundays, physical exercise was greatly reduced. Instead, recreational activities and occupational therapy were organised. Physical exercise took the form of 90 min of walking around the neighbourhood, or a coach outing was organised.

Dietary regimen

Another key feature of our PWRs is the diet. The diet was based on an average daily calorie intake of 1500 Kcal. We chose a Mediterranean diet [20], with no extra fats added. The food intake was subdivided into five meals. Breakfast, two main meals – lunch, and dinner – and two snacks were provided. The main meals started with fruits, then abundant cooked and raw vegetables. The nutritional value of the weekly food intake was carefully calculated to ensure a well balanced diet. We could not adjust calories in relation to sex and height because differential treatment among PWS patients is very badly tolerated.

Because food addiction involves also drinking, sometimes reaching dangerous levels, drinking was allowed only during meals and snacks. We estimated the daily water intake to be around 1.5–2.5 litres. Body weight was measured every morning before dressing.

Activities for the improvement of the patients' social and psychological development

Every day, at least 2 hours of psychomotor activity, or music therapy were organised.

Team games with a strong bias towards motor activities were the preferred option during psychomotor sessions. Hence motor skills, coordination, attention span, memory, and socio-psychological skills were all stimulated. These activities represent an important but difficult to quantify calories-burning factor. Last but not least, the patients deeply enjoyed them.

Breathing exercises, learning rhythm, dance, singing, and playing instruments were the main features of the group music therapy sessions. Both psychomotor and music therapy are aimed at improving social and behavioural development, while offering patients an enjoyable activity. On these occasions, group dynamics were studied by our psychologist [21] and appropriate measures were taken to further enhance bonding. These activities helped each individual to develop spatial self-perception and motility [22]. At the same time, patients benefited from relaxation, after hours of considerable physical fatigue and psychological stress.

Dual-energy X-ray absorptiometry (DXA)

A whole body dual X-ray absorptiometry (Hologic, Bedford, MA; Discovery A model) for body composition analysis was performed at the beginning and at the end of one PWR only. On the eight patients attending the PWR – four males (Average age 25) and four females (Average age 32) – the examination was performed at the same time during the day.

The elaboration of data was performed utilising Hologic software [23].

The bone mineral composition (BMC), the fat and lean mass volumes were evaluated.

Statistical analysis

Data were analysed using the statistical programme SPSS v. 16.0. The patients' data was expressed as

mean ± standard error of the mean (SEM). Regression lines shown in Figure 2 are the best curves fitting the observed data, and were calculated using a curve estimation analysis (law of diminishing returns) which takes into account the predicated values and residuals. Regression lines shown in Figures 3–4 were analysed using ANOVA test. In all the analysis, a p-value < 0.05 was regarded as significant.

Results

PWS patients taking part in the rehabilitation programmes

During the period under review, a total of 27 PWRs were organised by the institute with an average of 4 PWRs/year. This frequency has been systematically maintained since 2006. The patients were treated by our team over 6 years with an average of 7.2 patients/PWR (SEM 0.6). None of our patients participated in other rehabilitation programmes during the course of the year.

Thirty-five patients (71.4%) attending the institute were adult, while 14 (28.6%) were adolescents. The latter had a mean growth variation of 4.8 cm from the first to the last PWR attended (SEM 1.4). On arrival, 47 patients (96%) were under medication and their respective drug-schedules were maintained during their stay, or slightly modified, according to their needs: five patients (10%) were treated with benzodiazepines, 12 (24.5%) with neuroleptic drugs and 5 (10%) with both; 11 patients (22.5%) were treated with anti-epileptic drugs. Hence in total, 67% of the patients were treated with psychotropic drugs. Four patients (8%) were treated for Parkinsonism. Only five of them (10%) were treated with growth hormone (HGH) during the study, and 8 (16%) with oral hypoglicemics; 8 (16%) female patients were treated with sexual hormones.

Weight loss and PWRs duration

At the beginning of our study, the cycles lasted a maximum of 2 weeks. During these periods the patients suffered psychological strain, as measured by their non-compliance to physical exercise. A sharp decline in therapeutic compliance during the second week was unavoidable as evidenced by an increased incidence of temper tantrums. This occurred despite the fact that educational and physical activities were performed in small groups, and that the proposed diet was not excessively restrictive (1500 Kcal/day). We obtained satisfactory compliance lasting 3 weeks when we introduced suitable entertainment, and physical exercises were balanced with adequate rest periods. We managed to extend the therapeutic cycles to 4 weeks from 2006, when organised psychomotor and music therapy were introduced.

Data analysed by the one-way ANOVA statistical test showed that cycles of 15, 21 or 26 days led to a daily body weight loss of 0.19 kg (SEM ± 0.37), 0.22 kg (SEM ± 0.42) and 0.26 kg (SEM ± 0.23), respectively. We frequently registered days of patient's complete inactivity – due to minor seasonal illnesses – , and weight gain (most likely due to water retention), causing an excessive spread of data, compromising the statistical value of the results. However, the weight loss progression (Figure 1) clearly indicates that body weight loss strictly depends on PWR duration.

Moreover, while in the 2-weeks (33 patients) and 3-weeks (28 patients) PWRs we observed a final decrease of compliance, and subsequently of weight loss, in the more recent 4-weeks (17 patients) PWRs a substantially linear weight loss was maintained during the whole training programme (Figure 1).

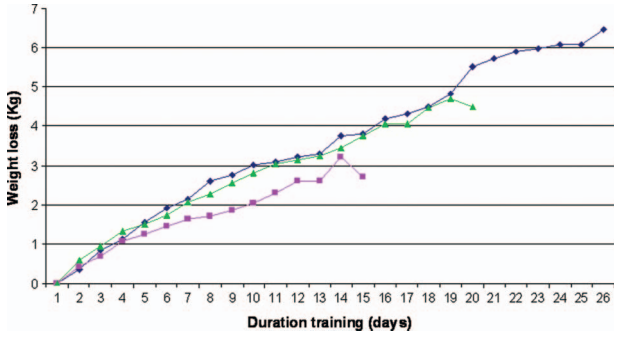

Figure 1. Duration of the training cycles and weigh loss in PWS patients. A comparison between patients attending cycles of 2 (■-■-■), 3 (▲-▲-▲) and 4 weeks (◇-◇-◇) shows that the body weigh loss (kg) recorded daily in patients is similar and dependent on the duration of the sessions. Data were analysed by one way ANOVA test.

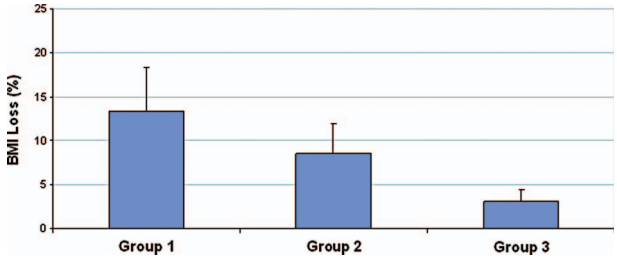

Figure 2. BMI loss in percentage of treated PWS patients is proportional to attendance. The shown BMI values were calculated as BMI loss percentage: 100-((BMI at the last discharge/BMI at the first admission)*100). PWS patients were subdivided into 3 groups, according to the PWRs attendance: Group 1, attendance of at least three consecutive PWRs; group 2, at least 3 PWRs, but not consecutive; group 3, less than 3 PWRs. Data are expressed as mean ± SEM.

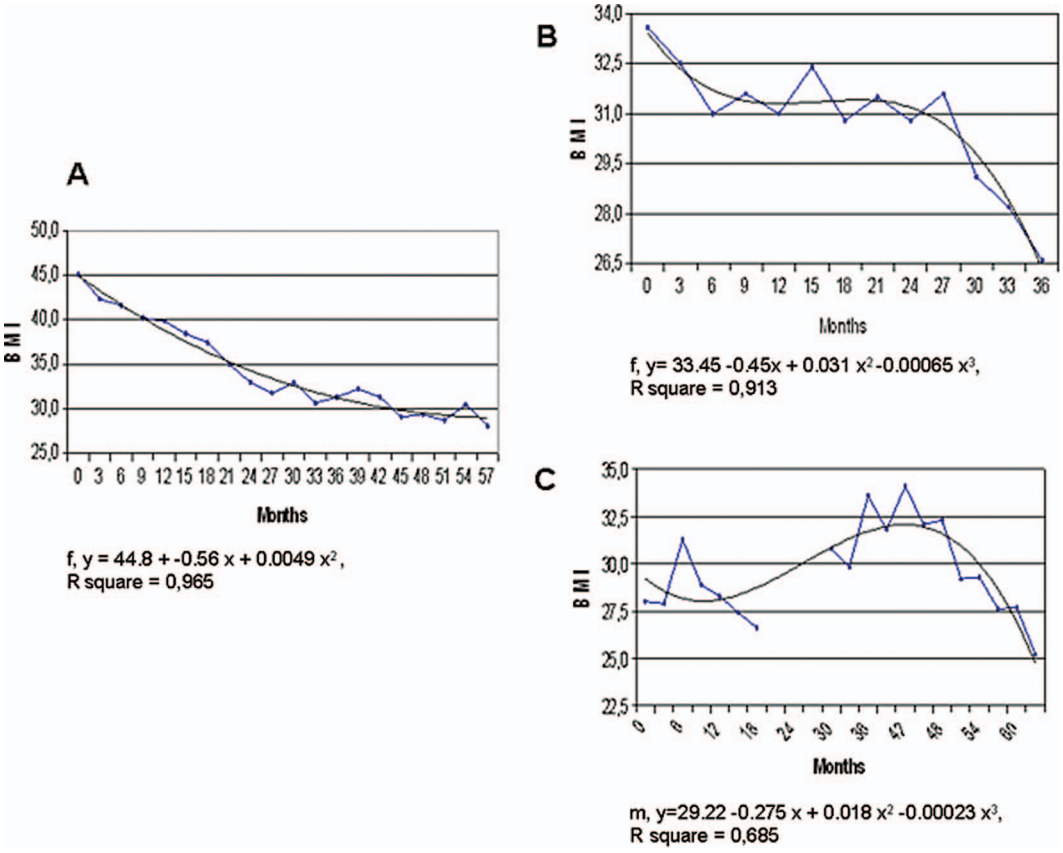

Figure 3. BMI variation in patients attending the majority of PWRs. The figures show the BMI variation from the first admission to the last discharge of 3 patients (A–C). Patient A (female, 23 years old), patient B (female, 35 years old), patient C (male, 21 years old) underwent therapy for 91%, 87%, 80% of the programmed sessions, respectively. Regression lines were significant with a $p < 0.005$ using the ANOVA test.

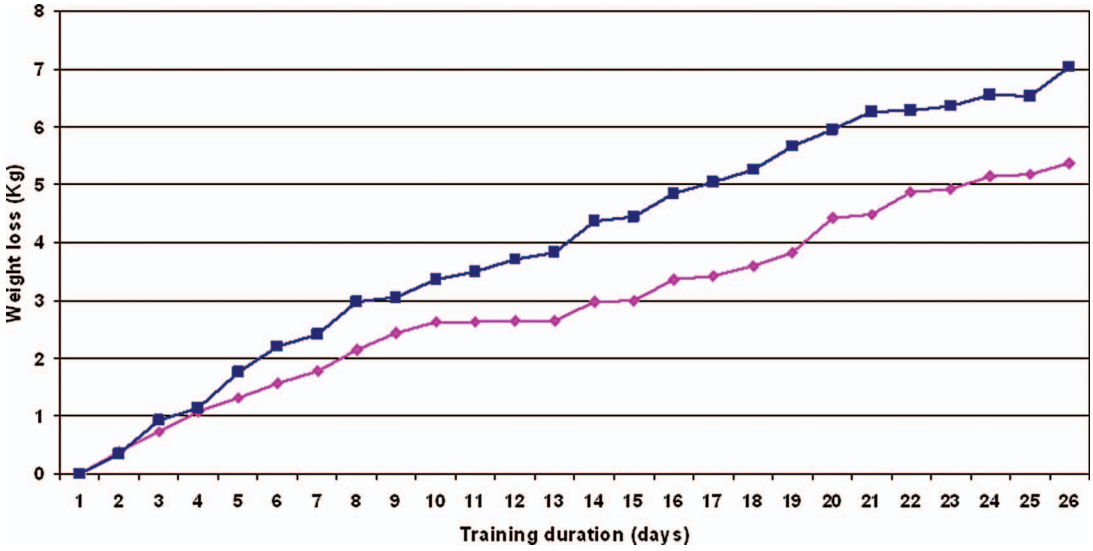

Figure 4. Gender difference in body weight loss in PWS patients during a 4-week PWR. The body weight loss was followed for 4 weeks in 11 male and 6 female patients. A significant gender difference was observed. ($p < 0001$) The results show the mean body weight loss measured daily since the patient's admission. Data were analysed by one way ANOVA test. Squared line ■-■-■: males; diamond line ◇-◇-◇: females.

At every PWR, an average loss of 5.3 kg, corresponding to 2.1 BMI units (SEM 0.2), was observed in patients who completed the 26 days cycle. These data indicate that the daily weight loss improved over the years, and that currently the treatment duration can be lengthened up to 4 weeks

without the previously experienced final loss of compliance.

Weight control and attendance to PWRs

During the examined period, the 49 examined patients showed at their last discharge an average BMI reduction of about 2.5 points (6.6%) compared to the BMI recorded on their first admission (Table I).

We recorded a heterogeneous attendance. In order to better understand the effect of the therapy in correlation to the attendance, we subdivided the population into three groups. Group 1 (8 PWS), included patients with an attendance of at least 3 consecutive PWRs; group 2 (12 PWS), included patients attending at least 3 PWRs, but not consecutively; group 3 (29 PWS), included patients attending less than 3 PWRs. The effect of the participation to therapy in each group is reported in Figure 1. The percentage of BMI loss recorded in frequently treated patients (group 1: 13.4%, SEM 4.9) was higher than in group 2 patients (group 2: 8.5%, SEM 3.5), and significantly higher than in less frequently treated patients (group 3: 3.1%, SEM 1.3).

To confirm these data, we analysed the BMI variation against the training duration in three PWS patients who attended 91%, 87%, and 80% of the sessions. As shown in Figure 2, in all three patients the BMI recorded at the end of the treatment was significantly lower (8.9, $\pm$ SEM 4.2) than at the beginning. Attendance of more than 80% of the programmed PWRs ensured efficient weight control with a rapid and constant decrease of BMI in time (Figure 3A). A less frequent or an interrupted attendance to sessions was still effective, but the BMI showed a reduction in time fitting a cubic regression line (compare Figure 2A with 2B, 2C).

A telephone survey of nine patients who never attended our sessions or only once – but not in the last 2 years – was performed. It showed that their current average BMI is 44.9 (SEM 2.9), while it was average 42.4 (SEM 2.9) when they last left the institute. Patients attending our PWRs with greater frequency showed an entrance 38.5 BMI (SEM 1.7), and currently display a 35.2 BMI (SEM 1.6).

These data clearly show that our combined therapy is effective in BMI reduction, and that the weight loss in the treated population is proportional to the rehabilitation programme attendance.

Weight loss distribution as determined by X-ray densitometry (DXA)

DXA analysis was performed twice, during 1 PWR only, at the beginning and at the end of the cycle (Table III). Despite the fact that the two evaluations were performed only on a few patients, the DXA analysis gives a clear idea of the weight reduction distribution.

The fat loss was of 1976 g (SD 574). The lean mass loss was on average of 2283 g (SD 1262). Therefore, the total loss during this time frame was on average 4250 g (SD 1511).

The lean mass accounts also for the liquid content of the tissues. The software in use did not allow to distinguish between muscle and water. Considering the maintenance or improvement of motor skills and endurance during the PWR, it seemed logical to account for the decrease of lean mass to water loss, and therefore to state an equal distribution of weight loss between fat and water mass.

Gender difference in body weight loss

The effect of a prolonged PWR on weight control was analysed in male and female PWS patients.

Table III. DXA evaluation at the beginning and at the end of a single PWR.

Sex	Δ BMC	Δ Fat	Δ Lean	Δ Lean + BMC	Δ Total mass	Δ % Fat
F	−23,6	1593,9	1729	1705,3	3299,2	0
F	−52,7	1630	684,3	631,5	2261,6	0,6
F	4	991,6	3368,2	3372,2	4363,9	−1,4
F	−1,1	2151,4	3901,2	3900,2	6051,5	−1,1
M	22,7	2257,6	1543,8	1566,5	3824,1	0,6
M	−55,4	1864,9	794,7	739,3	2604,1	1,6
M	64,5	2740,6	2710,1	2774,5	5515,1	−0,1
M	−28,1	2583,1	3533	3504,8	6088	−0,2
AVE	**−6,6**	**2031,3**	**2362,2**	**2355,6**	**4386,9**	**0**
SD	**42,9**	**597,6**	**1342,5**	**1361,6**	**1578,5**	**1**

Four females and four males of a single PWR were evaluated. The bone mineral content (BMC) did not show any significant variation. All of the patients showed an equal distribution of water and fat loss, with little or no variation of fat percentage at the first and last evaluation. All values are expressed in grams. AVE = average; SD = standard deviation.

Figure 4 shows the daily loss of weight recorded in the 6 female and 11 male subjects who attended the 4 weeks PWRs. Statistical data analysis shows that body weight loss positively correlates with the duration of the programme in both male and female patients. The calculated correlation coefficients of the regression lines were $R^2 = 0.975$ and $R^2 = 0.973$ for female and male, respectively. A one-way ANOVA test proved significant in both groups with a p value < 0.001. The two regression lines were significantly different as measured by Euclidean distance statistical test ($p < 0.001$).

Indeed, females lost weight at a slower pace (mean 0.28 kg/day $\pm$ SEM 0.29) compared to male patients (mean 0.4 kg/day $\pm$ SEM 0.4). Females lost an average of 1.8 BMI points (SEM 0.2) (4.3 kg) at every cycle, while males could reach a weight loss of 2.9 BMI points (SEM 0.3) (6.5 kg).

It is known that genetic alteration in PWS leads to dysfunction of several hypothalamic centres and to growth hormone deficiency. To our knowledge, no information is available on the effects of gender related physiology in PWS hyperphagia. Our data seem to show the existence of such mechanisms leading to more efficient body weight loss in male than female PWS.

Discussion

The model described has been applied to teenage and adult PWS patients. This age group shows the worst maladaptive complications [17,24], with morbidity and mortality mainly impaired by obesity [3]. To the best of our knowledge, the strategy described here – a 4-week residential rehabilitation programme, repeated four times a year – is a unique model for the weight control and rehabilitation of obese patients with mental retardation. The treatment is not alternative, but complementary to the underlying drug therapies. It is based on a controlled but not too restrictive diet complemented by increased physical exercise and enhanced by educational and recreational activities.

From the beginning, our main problem was to achieve and then maintain the patient's compliance with the rehabilitation programme all through its duration. As shown in Figure 1, initially the decline in compliance to physical exercise was already evident during the second week, resulting in a significant weight-loss slowdown.

It is widely accepted that the weight maintenance or loss in PWS patients is achieved by strict calories control [2,25]. However, the restricted calories intake may lead to physiological and psychological stress in patients. Since the first PWR we thus chose a 1500 Kcal/day diet, which is far more than what is usually allowed to PWS patients in rehabilitation treatments (e.g. Wenger SL et al, 1987 [26]). The abundance of cooked and raw vegetables and fruits, and unrestricted access to water during meals, resulted in a diet with a low caloric but significant volumetric intake. This increased the feeling of satiety, helped to keep anxiety low and dramatically enhanced tolerance to the enforced regimen.

The dietary regimen was slightly modified over the years, not only by improving the volume/calories ratio but also by inverting the usual serving order of the courses. Meals started with fruits, then vegetables were served, etc. Optimal nutritional value of the meals continued to be a priority. Moreover, there was an emphasis on teaching good table manners, thus avoiding behavioural excesses. This facilitates acceptance of PWS subjects by society at large, and helps their own psychological self-containment. We always advised families at home to continue to insist on good social behaviour at mealtimes.

By optimising dietary strategies, and adding entertainment activities, we could obtain endurance up to the third week, despite a decrease of weight loss during the last week.

It must be stressed that activities have always to be wisely mixed with appropriate rest-times, since fatigue and stress can provoke temper tantrums and episodic loss of therapeutic compliance, typical of PWS. They may affect the single patient and destabilise the whole group. Their prevention, mediated by these activities, is therefore crucial.

Definitive progress was achieved with the introduction of another key-feature of the PWRs: music therapy and psychomotor activity. This allowed us to prevent the compliance fall during the third week and to extend PWRs up to 4 weeks. We continued to observe a regular daily weight loss, and maintained full compliance to the strict daily schedule, from the first to the last day. Moreover, the efficacy of these activities on patients' mood during the treatment period was evident. They were distracted from their obsession with food; their self-esteem improved; feelings of friendship and team spirit were established.

The current protocol is the result of many years of practice and follow-up. It has evolved through successive stages, each having allowed the prolongation of PWRs of 1 week, up to the actual 4 weeks. We could thus consider each step as the control group of the following one, in which a compliance gain was achieved (see Figure 1): after first attempts, establishing the basic principles of our approach – not restrictive diet and the exercise as the main means to lose weight – the second stage mainly acted on diet, alimentary behaviour and non-structured entertainment activities; the third stage performed the introduction of regular, daily psychomotor activities and music therapy.

It is our belief that a PWRs lasting longer than the currently organised 4 weeks, would show a fall in patients' compliance, and that groups of more than 10 patients would be hard to manage, due to the complicated social dynamics.

PWS patients are adverse to physical activity. To ensure the patient's commitment to the exercise schedule, a combination of strategies needed to be implemented. Fun, teamwork, and competition, are outstandingly important triggering factors for stimulation and motivation. At the same time excessive fatigue must be avoided otherwise this would lead to tantrums and refusals. Surprisingly, motor activities performed on machines were welcomed by patients: they took pride in their achievements and their self-esteem improved. Two hours of extra psychomotor therapy and music therapy were added. Considering the difficulties encountered in achieving these results (see Figure 1), and noting at the same time an increase in the patients' commitment to the PWRs over the last few years, we consider these notable milestones.

A daily physical exercise of 6.5 h could seem unsustainable and excessive, if we think to normal obese patients, but we shall remember that every exercise was performed at a slower speed than normal, and with frequent interruptions. Where normal obese people would have shown an energy expenditure of about 3400–4000 Kcal for the daily activity described, in PWS, the calorie expenditure seems to be reduced by about 20% [27]. On the one side, some exercises cannot be maintained at normal speed (see methods), thus leading to lower energy expenditure. On the other side, psychomotor therapy, which can certainly lead to important calorie expenditure, is alternated with music therapy, a much weaker calorie-consuming activity. This explains why we achieved a daily weight loss of only 0.26 kg. We now reasonably argue that about half of that was water (see Results and Table III). Therefore, we can state that, despite appearances, the physical exercise daily performed by patients results in a real energy consumption of about 1000 Kcal exceeding the basal metabolic index.

The lean mass volumes detected by DXA involve also the extracellular water contained in it. PWS is also affected by a well-known disturbance of water metabolism [28]. Therefore, it is conceivable that the lean mass loss observed (Table III) could be accounted for by a water loss instead of a real muscle mass loss, the latter being in contrast with the patients' stability or improvement in endurance to exercise, and progressive weight decrease over years shown in the high-attendance group (group 1). A recent publication hypothesise that the lymphedema risk can be largely underestimated in PWS patients [29]. However, liquid retention is a well-known problem in PWS. GH treatment, instead, is reported to benefit the fat/lean mass ratio in adult PWS, but also the liquid metabolism [6,7]. The typical PWS body composition was widely studied in children. The decreased extracellular-to-intracellular ratio was found to be less in PWS, and this constitutes another key-feature of PWS body composition, together with the fat mass. Body composition was found to be related to both GH function and to physical activity [30]. Therefore, it is not surprising that the intense physical activity performed during PWRs was found to improve the BMI by decreasing both the fat mass and the extracellular-to-intracellular water ratio.

The average loss of 5.3 kg at every PWR, corresponding to 2.1 BMI units (SEM 0.2), can be maintained in the interval between cycles, if the family or/and community adhere to our guidelines, basically based on dietary discipline and on maintenance movement. Unfortunately, this is not always the case. We found that best results were obtained in those patients attending a daily care centre in coordination with our institute.

Compared to other approaches to these kinds of illnesses, our programmes achieve their principal aims keeping patients 'anchored' to their families/communities and boosting their overall wellbeing.

Dykens MD [17] noticed behavioural gender differences in her PWS population. We also found that weight loss is sex-matched (Figure 4), even if we did not have sufficient data of statistical significance. Females seem slower in losing weight during PWRs. We did not find any correlation with sexual, growth hormones, and psychotropic drugs. A hypothesis could be based on the difference in muscle mass between males and females, considering that physical exercise greatly contributes to weight control.

In our adult PWS population, for unknown reasons HGH therapy is seldom administered in adulthood, and if it is, only at very early stages. Reasons are likely to be cultural, and we will probably see a slow increase of its use over the next few years. On the other side, psychiatric therapy was often over-administered. After careful analysis of the clinical history and evaluation of actual clinical conditions, we often rediagnosed the psychotic symptoms, reformulating the diagnosis from psychotic to disthymic disturbances. Moreover, the sedative effects of benzodiazepines can hinder patients' activities and induce drowsiness, reducing therapeutic compliance. Their dosage is therefore very often reduced during their stay without any fresh outbreak of the symptoms.

One female patient presented with a presumed PWS diagnosis, lacking any molecular confirmation. She was eventually found not to be affected by PWS, but by another genetic obesity with mental retardation, still under evaluation. Therefore, she was not

included in this study. However, she responded well to the PWR, and showed weight loss comparable to other PWS females. In spite of the fact that our rehabilitation cycles are solely focused on PWS, the same approach could be used to benefit other genetic obesities [31].

What is really new, to the best of our knowledge, is that the weight loss – and in some cases the weight control – in older teenagers and adult PWS patients could be achieved by periodical (4/year) and prolonged (4 weeks) disease-customised residential treatments without strict dietary restriction. For these patients, who generally manifest a great resistance to motor activity, and are therefore hard to distract from hyperphagia, we obtained full compliance on a tight daily training schedule, working on their social development and improving their quality of life, at least during their stay.

We are currently focusing our attention on the following which will be addressed in further studies: the quantification and better organisation of music and psychomotor therapies efficacy, the assessment of patients' muscular strength and motor skills [32], genotype-behaviour differences, and the improvement of weight maintenance during intervals of PWRs.

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