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ORIGINAL ARTICLE

Nutritional phases of Prader-Willi syndrome

Fases nutricionales en Síndrome de Prader-Willi

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What do we know about the subject matter of this study?

This syndrome is the most frequent cause of genetic obesity. Before obesity and hyperphagia, the patient goes through a notorious feeding difficulty and apathy with secondary malnutrition, progressing to relative eutrophy and feeding behavior similar to her/his peers without the syndrome.

What does this study contribute to what is already known?

In this Chilean case series, the nutritional phases described by Miller et al. in North America are replicated, reproducing the transition from feeding difficulty to hyperphagia as the individual's age increases.

Abstract

Prader-Willi Syndrome (PWS) is the most common cause of genetic obesity. Hyperphagia and obesity are the most associated concepts with this condition. However, undernutrition secondary to severe hypotonia and feeding difficulties is the predominant initial feature. **Objective**: to reproduce and communicate the nutritional phases on a series of Chilean cases with PWS. **Patients and Method:** Cross-sectional study in which clinical records of PWS individuals under nutritional control at the Clínica Santa María in Santiago, Chile between 2017 and 2018 were analyzed. The anthropometric references of the World Health Organization were used to carry out the nutritional assessment. The classification into nutritional phases was according to the Miller criteria. **Results:** 24 patients from infants to adults were included. All children aged under 9 months were in phase I and had malnutrition or were eutrophic; those between 9 and 25 months were classified in phase 2a; patients between 2.1 and 4.5 years were distributed between phases 1 and 2 and 66% were eutrophic; those between 4.5 to 8 years, 80% were in phase 2a and 2b and obesity begins to appear, and patients over 8 years of age, 75% were in phase 3 and all are overweight or obese. There was an association between nutritional phase and age but not between it and nutritional status. **Conclusions:** In our series, the nutritional phases described according to age were reproduced according to those internationally described. There was no association between nutritional status and age.

Keywords:
Hypotonia;
Undernutrition;
Feeding Difficulties;
Obesity;
Hyperphagia;
Prader-Willi Syndrome

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Introduction

Prader-Willi Syndrome (PWS) is the most frequent genetic cause of secondary obesity. It is produced by a lack of expression of a group of genes in chromosome 15 of paternal origin, specifically in the region 15q11-q13, which can be due to a microdeletion of this chromosome (60-70%), to maternal uniparental disomy, that is to say, the inheritance of 2 copies of the maternal 15q11-q13 segment (30-40%), and in less than 3% of the cases, it is due to mutations of the regulatory genes of the genomic imprinting.

This syndrome is an example of the genomic imprinting disorder as the defect of chromosome 15 of paternal origin produces PWS, however, the affection of the same genes of the maternal chromosome causes Angelman syndrome, whose phenotypic characteristics are completely different. Its incidence is 1/10,000-30,000[1], affecting males and females indistinctly. In Chile, in 2005, Cortés et al[2] published a clinical, genetic, and molecular characterization of 45 patients evaluated at the Diagnostic Center of the Institute of Nutrition and Food Technology (CEDINTA), demonstrating that the clinical criteria of Holm[3] were useful and the distribution of genetic causes was similar in our population.

Traditionally, this syndrome is associated with severe obesity that is very difficult to manage. However, few are aware of the phases before this obesity during which it is possible to intervene to avoid or attenuate this secondary obesity[4-5].

Individuals with this syndrome present severe hypotonia throughout their lives but go through different nutritional stages, starting with an important feeding difficulty due to weak sucking with consequent poor weight gain and secondary malnutrition and complete apathy when being fed. Subsequently, a phase of normalization of appetite and gradual weight gain and development of hyperphagia begins, with the consequent frequent and severe obesity if no preventive measures are taken.

Other characteristics of the syndrome are[1] short stature, hypogonadism/hypogonadotropic hypogenitalism more evident in males due to the presence of cryptorchidism, central apneas, delayed psychomotor development, behavioral alterations, among which rigidity and tantrums that are difficult to manage, and skin picking disorder and obsessive behaviors. Among the most characteristic morphological alterations are almond-shaped eyes, narrow bifrontal diameter, thin upper lip, thick saliva, dry mouth, enamel hypoplasia, and small feet and hands, among others. Regarding psychiatric characteristics, anxious, psychotic, and autism spectrum disorders are correlated with genotype, which are more frequently described in uniparental disomy disorders[6].

In 2011, the nutritional phases of PWS[7] were described, the result of a follow-up study of 82 individuals with the syndrome and 84 of their siblings in which the natural history was observed regarding clinical, anthropometric, metabolic, and laboratory parameters, correlating them also with the use of growth hormone. Seven nutritional phases were identified with five major phases and two sub-phases.

Knowing the nutritional phases of the syndrome makes it possible to analyze all the phenomena that occur before this obesity develops, thus anticipating and attempting to modify the natural history of the disease, preventing or at least attenuating the severe obesity for which the syndrome is widely known.

The nutritional phases are described below:

Phase 0 (prenatal): These children are born weighing 20-25% less than their siblings without the syndrome, but there is not necessarily intrauterine growth retardation; decreased fetal movements are described during pregnancy, and there are no ultrasonographic markers that allow prenatal diagnostic suspicion.

Phase 1a (0-9 months): Feeding difficulties characterized both as a sucking disorder and apathy to be fed are predominant. These newborns are usually in the malnutrition range with weight-for-length compromise, considering the genetic short stature, which is more accentuated towards the second year. Most of them will require, at least during the first weeks of life, nasogastric tube feeding or the use of special bottle niples and feeding techniques. Speech therapy support at this stage is essential.

Phase 1b (9-25 months): They begin to feed similarly to their peers without the syndrome, begin to grow closer to the median of the growth curve, without satiety disturbance.

Phase 2a (2.1 to 4.5 years): This phase precedes hyperphagia and is a crucial time when parents should have already implemented preventive measures, education, and motor stimulation to prevent the next phase. An increase in weight-for-height is described, which correlates with an increase in fat mass, considering that muscle mass is always decreased.

The occurrence of this will depend on the hypotonia degree, the initiation of growth hormone administration, as well as therapeutic interventions such as physiotherapy and occupational therapy. This period is easy to detect by following the growth curve, with an increase from below the median to above it.

Phase 2b (4.5 to 8 years): Persistent weight gain for height and percentage increase in fat mass, but now associated with a gradual increase in appetite. It coincides with entry into the preschool system, so prevention and alerting the educational system is key. In this phase, behavioral management and the establishment

of what we call food security will be of relevant benefit so that the child does not reach morbid obesity.

Phase 3 (> 8 years): State of frank hyperphagia, they begin to show increased interest in food, crying, and tantrums related to visual or olfactory exposure or even just from hearing about food.

Phase 4: described in adults, generally older, who stop having an insatiable appetite, i.e., hyperphagia subsides, but not many individuals reach this stage.

The exact pathophysiology of hyperphagia has not yet been fully clarified. Alterations at the hypothalamic level of several hormones (growth, thyroid, and sex hormones) would explain part of their short stature and body composition[8]. However, other studies attribute responsibility to ghrelin, an intestinal hormone that stimulates appetite and lipogenesis, whose high levels have been demonstrated before the onset of hyperphagia and whose fluctuations seem to be closely related to nutritional phases[8]. Recent studies have shown a possible role of the snord116 gene in the altered maturation of this hormone[9].

On the other hand, neuroimaging studies have detected overactivation of the reward system and decreased inhibitory activity in response to exposure to photographs of food[10]. The lack of control over eating and insatiable appetite is usually triggered by the visualization and smell of food, generating nervousness, aggression, and tantrums. Behaviors such as stealing, lying, fighting, exchanging money, or even sexual exchange to obtain food have been described. Ingestion of pet food or from the garbage has also been frequently reported. Therefore, these individuals are at higher risk of gastrointestinal perforation, necrosis, and death related to uncontrolled ingestions[11].

Knowledge of this syndrome has greatly helped to understand what are and how the various mechanisms that influence the genesis of obesity during childhood interact.

The objective of this paper is to report a series of Chilean cases and to reproduce the nutritional phases in this syndrome in order to educate and sensitize the pediatrician and other health professionals involved in its care.

Patients and Method

Case series study in which clinical records of patients with PWS were reviewed. Most of the information was obtained from the data collected during the first consultation, in which demographic details (age, sex, place of residence) and information related to the genetic diagnosis were recorded, as well as anthropometric data (weight and height) and eating behavior evaluated only by anamnesis. For nutritional classification, the WHO guidelines were used, regardless of whether or not the patient was under treatment with growth hormone according to the Nutritional Evaluation Standard of the Ministry of Health (MINSAL)[12] and the Chilean growth curve of Alarcón-Pitaluga[13] was used to categorize birth weight adequacy according to gestational age. To evaluate the nutritional phases, the Miller classification (1a, 1b, 2a, 2b, and 3) was used, which considers growth, the presence of obesity, and eating behavior[7].

All patients with confirmed genetic diagnosis with PWS who attended Pediatric and Adolescent Nutrition Program at the *Clínica Santa María* between January 1, 2017, to December 31, 2018, were invited to participate. Parents signed informed consent and if the individual was older or equal to 13 years of age, informed assent was also requested. These documents and the research protocol were previously submitted and approved by the Scientific Ethics Committee of the *Clínica Santa María*. A descriptive analysis of the variables studied was performed. Categorical variables were described using absolute and relative percentage frequency distribution, and quantitative variables using mean, standard deviation, and range. Fisher's exact test was used to evaluate the association between categorical variables. Stata 13 software was used and a level of 0.05 was considered significant.

Results

At the time of the analysis, 24 patients who were under nutritional follow-up at the *Clínica Santa María* agreed to participate. There was a higher frequency of men (67%). The age range was wide (0-37 years), 83.3% of the patients were under 8 years of age. There was only one adult patient (37 years old) in the control group. See table 1 and 2.

Diagnosis

All individuals had a genetic diagnosis that confirmed the clinical suspicion, usually due to marked hypotonia and/or secondary feeding difficulties. 87.5% of them had an early diagnosis (during the first year of life), 16% of them during the neonatal period. In 20% there was a positive methylation test, which confirms the syndrome, but the exact genetic defect could not be determined. In 50% a microdeletion was determined and in 25% uniparental disomy, and in one case a defect of the imprinting genes was detected (4%).

Nutritional status and phase

Regarding perinatal history, 33.3% (CI 15.6%-55.3%) of the patients were premature or less than 37 weeks gestational age, 50% had a low birth weight (<

2500 gr), none of them weighed less than 1500 gr, and 41.7% were classified as small for gestational age (SGA).

There were no significant differences when analyzing the incidence of SGA according to the different molecular types (p = 0.760).

At some time during the neonatal period, 100% of the individuals required nutritional support with a nasogastric tube. None required gastrostomy.

Table 3 shows the distribution of nutritional aspects according to the age groups determined by Miller's nutritional phases as follow: all children under 9 months are in phase 1a or 1b; between 9 and 25 months, there is a greater dispersion between phase 1a, 1b or 2; between 2.1 and 4.5 years, 43% are in phase 2a; in the group of 4.5 to 8 years 40% are in phase 2b; and over 8 years, 75% of them are in phase 3.

Likewise, we can see the tendency of a transition from malnutrition predominating in 50% of children under 9 months to a group of subjects divided between eutrophy and obesity between 2.1 and 4.5 years of age, and 100% overweight and obesity in the group older than 8 years of age.

When Fisher's exact test was performed, there was a significant association between nutritional phase and age group, but not between age group and nutritional status.

Figure 1 shows that, with increasing age, the point cloud format moves diagonally from the lower-left corner (earlier nutritional phases and nutritional states associated with malnutrition) to the upper right corner (more advanced nutritional phases and nutritional states associated with obesity).

Table 1. Prader-Willi Syndrome Case Series

Patient	Sex	Age (years)	Age of diagnosis (months)*	Genetic alteration**	Use of Growth Hormone	Nutritional phase	Nutritional state***	Chilean Region
1	F	3	7	*Imprinting defect*	NO	1b	SP	Metropolitan
2	M	4	2	Uniparental disomy	YES	2b	EU	Metropolitan
3	F	7	2	Uniparental disomy	YES	2b	RD	Araucanía
4	M	4	4	Uniparental disomy	YES	2a	RD	Metropolitan
5	M	1	1	Deletion	NO	1b	EU	Ñuble
6	F	4	1	Deletion	NO	2b	EU	Maule
7	F	37	24	Uniparental disomy	NO	3	SP	Metropolitan
8	F	16	3	Undetermined	NO	3	SP	Metropolitan
9	M	3	0	Deletion	YES	2a	RD	Metropolitan
10	F	1	1	Deletion	YES	1a	D	Copiapó
11	F	9	2	Deletion	YES	3a	OB	Metropolitan
12	M	2	1	Uniparental disomy	YES	2a	SP	Metropolitan
13	F	7	5	Deletion	YES	2a	EU	Araucanía
14	M	2	2	No determinado	NO	1b	SP	Metropolitan
15	M	6	24	Deletion	NO	3	OB	Metropolitan
16	M	5	28	Deletion	NO	2a	OB	Metropolitan
17	F	2	0	Deletion	NO	1a	D	Metropolitan
18	M	2	1	Deletion	YES	1b	EU	De los Ríos
19	M	0	1	Undetermined	NO	1a	D	De los Ríos
20	M	10	2	Undetermined	YES	1a	SP	Metropolitan
21	M	3	3	Uniparental disomy	YES	2a	SP	Metropolitan
22	M	3	0	Undetermined	NO	1a	RD	Los Lagos
23	M	0	1	Deletion	YES	1b	EU	Metropolitan
24	M	0	0	Deletion	NO	1a	RD	Metropolitan

F: Female. M: Male. *0: diagnosis during neonatal period. **Undetermined stands for a positive metilation test, without determining the specific alteration. ***D: undernutrition, RD: risk of undernutrition, EU: eutrophic, SP: overweight, OB: obesity. Nutritional Phases: Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet Part A. 2011; 155(5) 1040-49.

50% of the patients were on growth hormone treatment at the time of evaluation. The age of initiation and duration of this treatment was variable for each individual. No significant differences were found in the phase and nutritional status between patients with and without growth hormone treatment ($p = 0.461$), nor with the different molecular diagnoses ($p = 0.76$).

All the individuals were beneficiaries of some type of therapy such as kinesiotherapy, speech therapy, and occupational therapy, among others, however, the intensity, regularity, and quality of these therapies varied greatly both individually and seasonally.

Discussion

In our series, it was possible to partially reproduce the nutritional phases described by Miller et al. after a follow-up of up to 10 years of 82 individuals with PWS analyzed in a North American collaborative network. Our study is a cross-sectional and descriptive one, without necessarily being a representation of the natural history of the disease. However, a relationship between nutritional status and age group was determined. In the future, we intend to analyze the data prospectively.

Several confounding factors may have influenced the lack of correlation between nutritional phase and age group:

The number of subjects is considerably smaller, but relevant to determine trends in a country like Chile. To our knowledge, no other country in Latin America has attempted to reproduce the nutritional natural history described in the North American population. Racial factors may be playing a role since the population studied by Miller was 90% white, 5% black, and 5% Hispanic.

Table 2. Description of the studied Prader-Willi Syndrone (PWS) patients

Age group		
0-9 months	4	(16.7%)
9-25 months	4	(16.7%)
2,1-4,5 years	7	(29.2%)
4,5-8 years	5	(20.8%)
> 8 years	4	(16.7%)
Gender		
Female	8	(33.3%)
Male	16	(66.7%)
Prematurity	8	(33.3%)
Birth Weight (kg)	2.410	(2072.5-2855.0)
Gestional age adequacy		
SGA	10	(41.7%)
NGA	13	(54.2%)
LGA	1	(4.2%)
GH treatment	11	(45.8%)
Genetic diagnosis		
None	5	(20.8%)
Paternal deletion 15q11-q13	12	(50.0%)
Maternal Uniparental Disomy	6	(25.0%)
Imprinting disorders	1	(4.2%)
Nutritional phase		
1a	4	(16.7%)
1b	7	(29.2%)
2a	7	(29.2%)
2b	3	(12.5%)
3	3	(12.5%)
Nutritional state		
Undernutrition	4	(16.7%)
Risk of undernutrition	2	(8.3%)
Eutrophy	8	(33.3%)
Overweight	7	(29.2%)
Obesity	3	(12.5%)

Cate: n (%), variables cuantitativas: mediana (percentil 25 – percentil 75). Confidence intervalo for the prematurity proportion: 33.3% (15.6%-55.3%). SGA: Small for gestational age; NGA: Normal for gestational age; LGA: Large for gestational age; Nutritional phases: Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet Part A. 2011; 155(5) 1040-49.

Table 3. Distribution of nutritional phase and state fase according to age group in Prader-Willi syndrome

Variable		< 2 years old		2 – 5 years		> 5 years		P-value*
Nutritional Phase	1a	3	(50.0%)	1	(8.3%)	0	(0.0%)	0.002
	1b	3	(50.0%)	4	(33.3%)	0	(0.0%)	
	2a	0	(0.0%)	5	(41.7%)	2	(28.6%)	
	2b	0	(0.0%)	2	(16.7%)	1	(14.3%)	
	3	0	(0.0%)	0	(0.0%)	4	(57.1%)	
Nutritional State	Undernutrition	3	(50.0%)	1	(8.3%)	0	(0.0%)	0.053
	Risk of undernutrition	1	(16.7%)	1	(8.3%)	0	(0.0%)	
	Eutrophy	2	(33.3%)	8	(66.7%)	2	(28.6%)	
	Overweight	0	(0.0%)	1	(8.3%)	2	(28.6%)	
	Obesity	0	(0.0%)	1	(8.3%)	3	(42.9%)	

*Fisher's exact test. Nutritional phases: Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet Part A. 2011; 155(5) 1040-49.

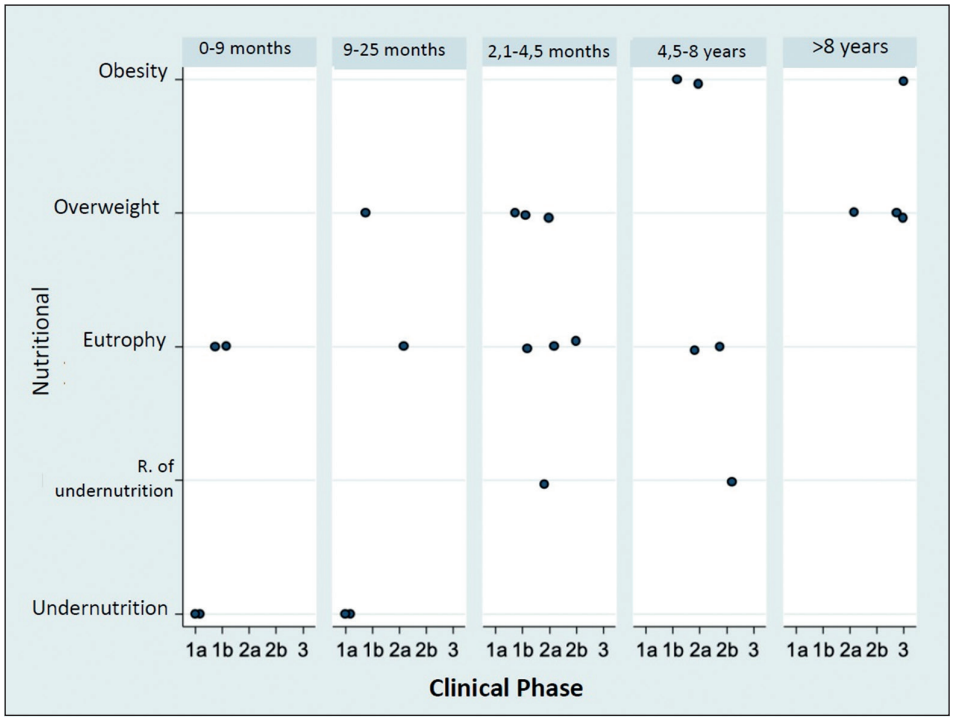

Figure 1. Relationship between nutritional clinical phase, clinical state and age groups in Prader-Willi syndrome. Nutritional phases: Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet Part A. 2011; 155(5) 1040-49.

To nutritionally evaluate the individuals, Miller et al. used the CDC standards, which represent the US population. We used the WHO standards, which are recommended for the Chilean population, due to the greater racial similarity, among other factors.

The categorization in each nutritional phase was assigned according to the clinical history and the phases described by Miller, by the same clinician with experience in the syndrome, which can be subjective. There are no specific scales to categorize the patient, except for the Dickens' Hyperphagia Questionnaire[14], which was not used in this study.

In this series, it was not possible to access more precise body composition studies such as bone density scan (DEXA), a factor that can play an important role in the nutritional classification, since it is known that the composition of the lean body mass is decreased, and fat mass is increased in these individuals[15].

In our series, only half of the patients had access to growth hormone, which is probably high for Chile due to its high cost and lack of coverage. Each patient started hormone treatment at different stages of their lives and it was not always maintained over time, so it was not possible to analyze this factor in depth. The younger patients in our series have received it earlier in life, because only recently have been demonstrated the benefits in PWS not only for improving height growth but also for improving body composition and physical strength, which results in a better quality of life and long-term metabolic improvement, also showing significant improvement in mental and cognitive development[16-17]. These benefits are both in hormone-deficient children and those without such condition[18]. Therefore, the selection of candidates is no longer based on demonstrating their deficit.

There are reference growth curves for individuals with PWS with[19] and without[20] growth hormone treatment, but for the reasons given above and in order to compare both populations, they were not used in this study for nutritional evaluation.

Our Chilean series describes a higher percentage of prematurity (33%), low birth weight (50%), and SGA (41.7%) than that described in the general Chilean population (7.8%, 26.1%, and close to 10%, respectively)[21].

In her paper, Miller describes that individuals with PWS had a significantly lower birth weight and gestational age than their siblings (2.8 vs 3.4 kg and 38.2 vs 39.2 weeks, respectively). An Italian multicenter retrospective cohort described on average half a kilo less in birth weight of individuals with PWS compared with their peers without the syndrome[22]. Likewise, another US multicenter study described a higher incidence of cesarean delivery (54%), 26% of preterm births, and 34% of low birth weight.

Our findings provide local information to warn

pediatricians and nutritionists in Chile and the region that this disease is characterized by marked hypotonia that transits throughout the individual's life with malnutrition that must be treated, followed by a relative eutrophy, since there is always a particular body composition characterized by a percentage of increased fat mass and decreased muscle mass, and if very early and active preventive measures are not established, it invariably leads to overweight and severe obesity[24-25].

Early diagnosis and transdisciplinary teamwork have been shown to significantly decrease the length of hospitalization stay, feeding tube days, and long-term obesity prevention[26].

We hope that we have contributed to broadening the knowledge about this syndrome.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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