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Prader-willi Syndrome: a Case Report

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Abstract

Prader-Willi Syndrome (PWS) is caused by different genomic alterations, all related to the inactivation of paternally expressed genes in human chromosome region 15q11-q13. This genetic condition appears not to be inherited, with an incidence of 1 in 25,000 births and a population prevalence of 1 in 50,000, with no differences due to gender nor ethnicities. Due to the fact that PWS is considered a rare disease, often its correct diagnose is delayed many years due to a lack of knowledge and understanding of its etiology by physicians at medical centers, in addition to the presence in this disease of signs and symptoms common to other syndromes, creating an additional challenge which may worsen the prognosis of these individuals.

In the present report we describe the case of a 22-year-old Spanish woman, diagnosed with PWS with a genetic study performed at the age of 7, even though the patient had shown the characteristic signs and symptoms of this syndrome since birth. We describe here the different phenotypes associated towith this condition at the different ages, its clinical and genetic diagnosis, and current therapeutic approaches.

With the intention of giving visibility to this Syndrome, we have also created a medical documentary entitled “Sindrome Prader-Willi" that can be seen in you tube at https://youtu.be/TJPTtKanRkw.

Keywords: Prader-Willi Syndrome, Rare disease, Chromosome 15 abnormalities, Genomic imprinting, Endocrine disturbances.

Introduction

Prader-Willi Syndrome (PWS) is a rare (estimate prevalence of 1/10,000-1/30,000) and usually non-inherited congenital disease, first described by doctors Prader Labhart and Willi in 1956 (1). With a similar incidence in males and females and all ethnicities, this disease is currently

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recognized as a multisystem and complex genetic disorder, mainly affecting the expression of genes, known as "genomic imprinting", located on chromosome 15 (15q11-q13 region).

There are three main subtypes, depending on the type of genetic alteration, recognized in PWS,. The most common type of PWS (65-75% cases) is caused by a "de novo" paternally inherited deletion of the chromosome 15q11-q13 region. Errors in genomic imprinting can happen during the production of both male and female gametes during gametogenesis, but only the loss of expression of paternal genes in this region is considered a type of PWS, whereas if the maternal chromosome is affected, an entire different syndrome, known as "Angelmans" (AS) is produced. A second type of PWS (20-30% cases) is caused by a maternal disomy 15 (when both chromosomes 15 are received from the mother, with no paternal chromosome 15 present). In rare ocassions, other types of PWS have also been observed, caused by defects in the genomic imprinting due to micro deletions or epimutations (1-3% cases) and translocation or rearrangements of the 15q11-q13 region. Currently, DNA methylation analysis is the only available technique capable of diagnosing and differentiating any of these subtypes of PWS.

Despite its low prevalence, PWS is considered the most common syndromal cause of life-threatening obesity, and the first recognized disorder linked to genetic imprinting in humans. It is also well known that its clinical manifestations change with age, starting with hypotonia and poor sucking as a risk for normal development during infancy. As the individual ages, other physical, physiological, cognitive and behavioral changes become evident and can be confused with signs of other unrelated disorders. These symptoms might include short stature, intelectual disabilities, compulsive behavior, psychosis, self-inflicted lesions, hypothalamic dysfunctions and endocrine abnormalities. Therefore. early diagnosis of PWS and a correct management of its associated complications by the appropriate physicians is crucial (1)

The purpose of this case study is to describe the clinical manifestations, genetics, and genetic testing associated with one case of PWS encountered in our medical facilities.

Our Case Study:

We describe here the case of a woman, currently 22 years old, first diagnosed with PWS at the age of 7 with the use of a genetic test.

Her mother remembers that fetal movements were rare during pregnancy, and once born, the baby presented poor sucking skills, low vitality, sleepeness and lack of interest for food. Childbirth was premature, at 35 weeks, with a body weight of 2.270 kg, 43 cm of length and a head circumference of 34 cm. The baby required asisted breathing and mask. Several days after birth, she was diagnosed with global developmental delay, neonatal hypotonia and per ventricular leukomalacia (by brain ecography).

We can observe in Figure 1 the development of this child with SPW at 5 months and 3 weeks of age. She could only hold this posture for a few seconds, despite the correction of her arms' position. A MRI of the brain did not show the existence of any lesions. Due to these clinical

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signs, including difficulties to suck and rare and weak crying, a series of therapies were initiated: physical therapy, body massages, psychomotric and stimulatory exercises. However, a definitive diagnosis had not been given yet. When the child turned one year old (Figure 2), an increase in apetite was observed, to the point of becoming excesive, with episodes of intense food obsesion and compulsion. The amount of food ingested without a stimuli to vomit, characteristic in this disease, caused moments of intense sickness in the young girl.

As the child development continued, the signs of hypogonadism became evident: premature breast development, lack of minor genital labia and clitoris. At a psycological level, this girl presented a low tolerance to frustration, frequent temper-tantrums, irritability and obssesive-compulsive behaviors, with insistence in repeting routines, skin picking and self-inflicted lessions. The delay in the psychomotor development was clear but it was erroneously atributted to leucomalacia. She displayed however, a notable ability to resolve puzzles and games with labyrinths, had an immense imagination, positive social relationships, and showed afection to other children and adults.

Several physical features characteristic of PWS were already observed in her infancy: oval head, narrow bifrontal diameter, almond-shaped palpebral fissures, thin upper lip with a small down-turned mouth, small hands and feet, with pointy fingers, wrinkled skin, thick saliva, ogival palate, new teeth overcrowding and hyper pigmentation in hair and skin. At a visual level, the child presented strabismus and needed to tilt her head to the side to be able to see straight forward (Figure 3). She also presented difficulties in pronunciation of some letters, specifically the articulation of the letter “R”, which was corrected with exercises done with a speech therapist. At a physiological level, the child presented the following features: an unstable body temperature, with oscilations ranging from less than 36C to more than 38C, a higher pain threshold of what it was expected for a child, and an X-ray of her lumbar spine revealed signs of a toracic-lumbar scoliosis of 3 degrees.

At about the age of 6 years and 8 months, a genetic study was requested by the endocrinology specialist, and PWS was confirmed in the child at the age of 7. The genetic testing consisted in the analysis of the methylation status at the SRPN locus using a methylation assay called “methylation specific multiplex ligation probe amplification” (MS-MLPA). This analysis showed the existence of a methylation pattern characteristic of PWS. The existence of a microdeletion was confirmed with FISH (Fluorescent *in situ* hybridation) using the SNRPN 15q11-q13 probe (Vysis). An analysis of the microsatellites in Genescan and amplified by PCR allowed for the detrmination of the methylation status by using several probes at the SRPN locus and other imprinted nearby genes , as well as other probes within the region. The study of the following markers located in the 15q11-q13 region [D15S542, D15S1035, D15S912, D15S18, D15S11, D15S113, D15S97, D15S128 and D15S1233 GABRB3] indicated that the deletion was located between breakpoints BP2 and BP3.

The treatment consisted of daily subcutaneous injections of the GH hormone (recombinant somatropin, 1.2 mg). At the beginning of the treatment, the patient was 7 years and 3 months old,

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weighted 32.4 kg and measured a height of 118.5 cm (body index of 23.07 Kg/m^2). After seven months of treatment, her weight had decreased to 31.5 kg and her height increased to 125 cm (body index of 20.16 Kg/m^2). Some of the observed side effects of this treatment were an increase of mialgias in both body extremities, arms and legs, which decreased significatively once the GH dose was also progresively reduced. After a year of treatment, however, interruption of this treatment was considered due to the presence of a scoliosis which was becoming more and more acute, as detected in the X-ray exams (initial increase from 3 to 8 degrees, with a change to 18 degrees in 24 months)

Discussion

Early diagnosis of Prader-Wili Syndrome is fundamental to determine and anticipate its development, allowing doctors to recommend initial stimulation techniques, prevention and treatment therapies for obesity, and stimulate nutritional habits, etc. Additionally, this early intervention allows for avoidance of the use of invasive tests at a later time (such as muscular biopsies, gastro copies and neurological tests), decreases hospitalization time and gastric tube use and optimizes the study of endocrine dysfunction to prevent growth delays. Specifically, the decrease in the use of the gastric tube is of great importance in order to diminish language and speaking skill impairments in infants and children.
Currently, SPW is a difficult diagnosis, under diagnosed in children, rarely diagnosed before the age of two or three, and over diagnosed in obese adults with mental retardation (2) Holm V. A, et al developed in 1993 several criteria for the clinical diagnoses of SPW, being revised and updated in 2001. Considering that a genetic test is available at the present time, it is recommended to use the current clinical criteria today only as indicators to perform definitive genetic testing (3).

Clinical Diagnosis:
SPW presents several clear clinical characteristics correlated to the age of the affected person:

1- **Fetal and Neonatal Phase**: characterized by a decrease in fetal movement, increased incidence of C-sections, loss of muscle tone (central) and poor sucking in the infant, diminished weight gain. Infants often present genital hypoplasia (underdeveloped) and criptorquidia (undescended testicle)

2- **Early Childhood Phase**: psychomotor delays become more evident in this phase, associated with short stature due to low levels of growth hormone, and the development of hyperphagie (uncontrolled food seeking and eating). A Study found that the transition of the nutritional phases is complex and can be divided into seven steps (4,5). The affected children are usually happy, affectionate and social, with motor, cognitive and nutritional impairments. Physically, they show a characteristic phenotype with almond-shaped and clear eyes, triangular-shaped mouth, thick saliva, narrow bitemporal diameter, small hands with cone-shaped fingers and small equinovarus feet. The hypo pigmentation of the hair, eyes and the skin is common in those

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individuals who present SPW from gene deletion, due to the loss of a copy of the OCA2 gene (the alteration of the 2 copies of this gene produces tyrosinase-positive albinism) (6)

3-**Late Childhood and Adolescence Phase**: characterized by difficulties articulating certain words and letters, especially the "R" sound (rhinolalia), language and sleep disturbances. Hyperphagia also predominates during this phase, with an obsessive need of food, which in conjunction with a deficiency in growth hormone, low physical activity and hypotonia, increases in children the appearance of morbid obesity and its associated health complications (scoliosis, respiratory difficulties such as Obstructive Apnea Syndrome (SAOS), serious and repetitive infections, ventral hypoventilation, osteoporosis, lower bone mineral density) and in adults produces also hypertension, type II diabetes and cardiovascular disease, among other complications. Hypogonadism (central or primary) is also common in this phase, due to very low levels of inhibin B hormone, and consequently, progesterone, estrogen and testosterone. Adolescent males show lack of facial or body hair, low testicular volume and penis size and an immature body compared to their chronological age. Adolescent females could present lack of menstruation, oligomenorrea, abnormal menstruation and genital hypoplasia.

It is important to clarify that the hyperphagia is not directly due to an "excessive hunger", but to an obsessive-compulsive need to eat and a lack on satiety sensation. This is caused by a hypothalamic alteration in the arcuate nucleus, which is the center that regulates hunger and satiety, with a balance of hormones and peptides that specifically stimulate hunger in the absence of the satiety signal (7). Post-mortem studies in individuals with PWS have shown a reduction of neurons, specifically the ones involved with the production of oxytocin, in the hypothalamic par ventricular nucleus (8, 9). In addition, the obesity seen in Prader-Willi Syndrome is unique because it occurs with elevated values of ghrelin (peptide hormone that regulates appetite) that decrease less than expected after the ingestion of food. However, if this hormone is inhibited, the patients continue to feel hunger, which implies that this mechanism is not unique and it is more complicated that initially thought.

In these cases, these children should never be exposed to the use of food to reward or punish their behaviors, and the food itself should be in a controlled space with controlled access. The specialists in PWS suggest the creation of a "food safety" area at home, with the use of locks and keys in the spaces where food is stored, and with no access to money to buy food themselves, as well as the creation on an "emotional safety" area, with the establishment of clear expectations and limitations. Uncertainty should be eliminated with the prior planning of foods, explaining clearly when, where and what is going to be served. A failure to communicate these intentions can increase anxiety and behavioral problems in the children.

The behavioral phenotype of these patients affects the cognitive, emotional and social areas, producing a hypothalamic lesion. The analysis of neuroimages revel a decrease in the myelination and the size of the brainstem and a light ventriculomegaly and atrophy of the frontal cortex (10). Due to these changes, when these children are around 5-8 years old, they become more irritable, with very low tolerance to frustration, emotional lability, irritability, obsessive-compulsive behaviors, mostly related to food, with an inflexible and manipulative personality, tendency to lie and steal food, as well as a tendency towards physical actions on themselves such

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as scratches and self inflicted lesions. A recent study on brain connectivity explains how these self-inflicted lesions and obsessive-compulsive behaviors are due to an elevated connectivity in the prefrontal and primary sensor motor circuit, meaning that the response is not directly activated by the stimuli but mediated by an abnormal activity in these circuits (11)
Therefore, these children often have very strong tantrums, which reflect on their difficulty to control impulses and emotions. They respond negatively to changes in their routine and expectations, when in disagreement with someone, and often become frustrated under the rigorous controlled environment that might have to be established for them and that they cannot manipulate. Some early signs of a tantrum are: changes in their emotional verbal language, excessive motor activity and excitation, changes in facial expression and biting lips. These episodes of tantrums often end with sobs and strong cries.
Children affected with PWS also show very positive cognitive chacteristics. They have an excellent long-term memory and can learn with videos, illustrations and photographs very easily (perceptive organization). They are also very good at recognizing and evaluating spatial relationships, therefore very good at completing puzzles, reading with a very expressive vocabulary, great capacity for work and very hard workers when they want to achieve something. It is fundamental to not lose our most important outcome when working with children with PWS: to teach them to learn to be happy. If the pressure that we exerce on them is too high, we might only perceive frustration and pain (12)

4-**Late Adolescence and Adulthood Phase**: during this phase there is an increase in behavioral disturbances and psychological problems (psychotic and emotional), however, it is important to recognize and identify the phenotypical characteristics to avoid confusing general behavioral problems, such as stubbornness, lies, and laziness, with psychiatric problems. A study by Novell et al. (13) on functional brain connectivity found that obsessive compulsive disorders (OCD) were the mental disorders more prevalent (70%), followed by sleep disturbances (70%), psychotic disturbances (20%), general anxiety (20%) and phobias (10%)
Considering that these disturbances happen because of a dysfunction in the hypophysis (pituitary gland) of the hypothalamus, it is important to recognize the difficulty to correctly evaluate the source of these symptoms in an emergency medical center, due to the lack of vomits elevated pain threshold, elevated summarization (generation of physical symptoms of a psychiatric condition) and abnormal body thermoregulation.

Genetic Diagnosis:
The genetic diagnosis of PWS is confirmed by a laboratory blood analysis. The preferred DNA test is called a “methylation analysis”, which detects more than 99% of cases, including the major genetic subtypes. The technique of fluorescent *in-situ* hybridization (FISH) with specific probes allows identification of those patients with PWS due to a deletion, but it will not identify those who have PWS due to uniparental disomy or an imprinting error. This technique allows one to disregard the existence of translocation or other abnormalities in chromosome 15 (6, 14)
Different genetic alterations are possible, although the deletion or inactivation of paternal genes in the 15q11-q13 region of chromosome 15 is common to all. The lack of expression of the

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paternal allele of these genes is the origin of PWS. The principal candidate gene contributing to the PWS phenotype is SNURF-SNRPN. It is a bicistronic gene that codifies for two different proteins: (a) SNURF is encoded by exons 1-3, which produces a polypeptide of 71 amino acids, rich in arginine and unknown function; (b) SNRPN encoded by exons 4-10 with the production of the protein SmN, a spliceosomal protein involved in mRNA splicing, expressed in the brain and important in the survival of motor neurons (15, 16, 17)

The novo interstitial micro deletion of the paternally inherited 15q11.2-q13 region occurs in about 65-75% of the patients with PWS. The region can be roughly divided into 4 distinct regions that are delineated by 3 common deletion breakpoints (BPI, BPII and BPIII), which lie within duplications. The great majority of the deletions (92%) occur in between these breaking points, and with variable breaking length, generating two types of deletions: type I (40% cases), between BP I and BP III, and average length of 6.5 Mb (5.7 – 8.1 Mb range) and type II (60% cases), between BP II and BP III, spanning an average length of 5.3 Mb (4.8 – 6 Mb range). These recurrent common interstitial deletions are due to the presence of multiple copies of tandem repeated sequences at the common breakpoints flanking the deleted region. Several studies have indicated that individuals with deletions of type I show a more severe phenotype than type II. In addition, 8% of those with a deletion, have unique or atypical deletions, not type I or II, but of bigger size at other more distal breakpoints areas (BPIV and BPV) or of smaller size at regions different from the most expected, such as MKRN3 – ATP10 (18, 19)

Maternal uniparental disomy (UPD) is a less frequent chromosomal abnormality that leads to PWS. This accounts for approximately 20-30% of the cases, it is the second most frequent type of PWS and it happens when both chromosomes 15 are maternal, due to an error in the disjunction of the chromosomes during female's meiosis. Maternal UPD has been shown to be associated with advance maternal age (20). Trisomy associated with translocations may resolve to disomy 15 due to the loss of a chromosome and result in UPD in 50% of cases (21-23). Uniparental disomy could be due to a) a heterodisomy, due to non-disjunction of chromosomes during meiosis I, where the fetus inherit both chromosomes from the mother; b) an isodisomy, when the fetus inherit two identical chromosomes due to an error and non-disjunction during meiosis II; c) a partial form of hetero or isodisomy of chromosome 15 produced by interchange of material in meiosis I and posterior non-disjunction, or because a somatic recombination of the chromosome during the first stages of the zygote. In patients with PWS, heterodisomy is the most common type of uniparental disomy (24, 25)

Imprinting defects (ID) are a third type of chromosomal abnormality that can lead to PWS, which accounts for only 1-3% of the cases. This happens when paternal genes in the critical region of chromosome 15 are present but do not function due to imprinting. This defect could be due to: a) a random epigenetic error that establishes a genomic imprinting in the germ line or during the first stages of embryogenesis (26, 27) or b) in 15% of individuals with ID, due to a very small deletion (7.5 to 1000 kb) in the PWS IC region, located at the 5' end of the SNRPN

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gene and promoter (IC deletion). Of these, about half have an unaffected father, but carrier of the alteration, giving his descendants a 50% risk of inheritance (28-30)

Translocation is the less common form, with an incidence of less than 1%, with the production of chromosomic reorganizations of paternal origin or "de novo". These translocations are balanced with the breaking point in SNURF-SNPRN (31)

These genetic anomalies are often accidental, sporadic with a very low recurrence in families. To know the risk of recurrence in future pregnancies it is necessary to have previously identified whether or not it was caused by a deletion, a maternal uniparental disomy, an imprinting defect or a chromosomic reorganization (translocations). Deletions and disomies are considered aleatory and generally associated to a 1% of recurrence, whereas imprinting defects count to a 50% of recurrence. In this case, it is very important to have access to genetic counseling and prenatal diagnosis. In the case of translocations of paternal origin, the risk of recurrence can be ignored.

It has also been observed that patients with genotypes due to deletions have a greater tendency to depressive disorders with psychosis, whereas those individuals with uniparental disomies show symptoms related to the autistic spectrum: language alterations, perseverant thoughts, stereotypes, etc., however they demonstrate social interaction and skills when they need to obtain food. In these cases, their psychotic behavior is less predictable and more severe than in the individuals with deletion genotypes, they are given more psicopharmacos and therefore, they might show more negative side effects from this medication.

Treatment:

The use of a Growth Hormone (GH) Therapy is recommended after a multidisciplinary clinical approach, in conjunction with diet, environmental and life style changes. The use of GH does not correct hyperphagia, but when given early in life, has been demonstrated not only to increase height, lean body mass and mobility, but also to improve flexibility and reduce behavioral difficulties, improving cognitive functions, with an increase in the intellectual coefficient in those patients under this treatment sooner (32). It also has been shown to improve sleep quality and resting energy expenditure. This therapy is often continued during adulthood at a lower dose (20-25%) than for children. However, some side effects of this treatment on respiratory parameters have been recorded and should be take into consideration (33)

It is well known that PWS causes a deficit in the number of neurons responsible of oxytocin production in the par ventricular nucleus of the hypothalamus. Oxytocin participates in the regulation of satiety and our feeding behaviors, our social interactions and our emotional response, all very important responses that when altered can significantly affect the quality of life of the patients. A study by Miller *et al.* in 2017 found that the use of intra nasal oxytocin (IN-OT) at low dose is safe and can produce a reduction of satiety and improve socialization, decrease anxiety and compulsive behaviors (34). Another study has recently found that in babies younger than 6 months, the administration of IN-OT improved the suction feeding reflect in 88% of the cases after treatment (35)

The use of metformin can improve the sensation of satiety and decrease anxiety over food. A positive response to metformin might, however, depend on the degree of hyperinsulinism and

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intolerance to glucose (36). Another treatment, exenatide, a glucagon-like peptide-1 receptor agonist (GLP-1), has also been used to reduce appetite, contributing to weight loss, which also makes it an efficient treatment in PWS (37)

The attention to, and support of, patients suffering of Prader-Willi Syndrome should me multidisciplinary (38) The psychomotor delay and hypotonia can improve with a program of adapted stimulation and primarily with weekly sessions of physical therapy or psychomotricity. To correct language difficulties it is convenient to evaluate and re-educate the orthophony at an early age, improving the articulation and reducing the complications of deglutition and mastication. Based on a recent study by Gross *et. al.* (39) the high level of mortality by asphyxiation and lung infection in children and adults with SPW could be due, in part, to asymptomatic subjacent dysphagia. In the case of nutritional disorders, a psychologist and a nutritionist could help establish and monitor a nutritional regime (40). Lastly, but not least, The deformities affecting the vertebral column (cifosis and scoliosis) can be improved with sessions of physical therapy and on occasion, with a back support brace, foot arch supports and orthopedic shoes. Counseling , medication and group homes may help with some behavioral problems in childhood and adulthood.

Considering the wide range of genetic conditions associated with PWS and all its clinical features, updated information regarding the genetics and phenotypic characterization of individuals PWS is crucial for all physicians and will be helpful in recognizing patients that may benefit from further investigation and genetic screening, to anticipate complications associated with this rare-obesity related disorder (41).

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Foto 1.- Girl with PWS, age 5 months and 3 weeks. She could only maintain this posture for a few seconds.

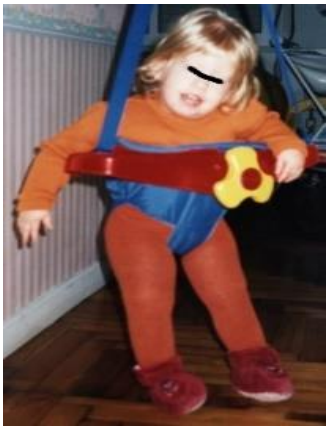

Foto 2.- One year old girl with PWS

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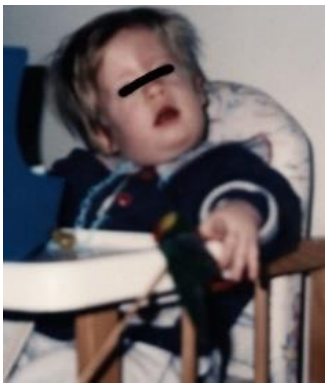

Foto 3.- Girl with PWS displaying characteristic PWS features: oval head shape, narrow face, small mouth, inverted lips, hypo pigmentation in skin and hair, small hands and feet, pointed fingers and estrabism, with tendency to lateral head movement to be able to look forward.