PRADER WILLI LIKE SYNDROME - THE NEW MEDICAL CHALLENGE

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Abstract

PraderWilli syndrome (PWS), the most common form of syndromic obesity, is characterized by a great phenotype and genotype variability. Most cases of PWS (approximately 70%) are determinate by deletions of 15q11-13 band on chromosome 15 received from the father; 28 % of cases appears due to maternal disomy. The imprinting center isolated mutations determinate less than 1% of cases. There are alsovery rare cases with unknown cause of disease, even if the clinical score indicate a positive diagnosis of PWS. Several studies mentionedother gene mutations that mimic PWS phenotype (PraderWilli Like syndrome) without involving chromosome 15. The present study aims to present 6 patients withPraderWilli Like syndrome (PWL syndrome) and also to indicate a strategy to establish the right diagnosis for them.We selected 3 girls and 3 boys, aged between 8 and 29 years old, who presented positive clinical score for PWS according to their age and negative genetic tests for the disease. We performed clinical examination and laboratory tests for all the patients. The patients were directed to other advanced genetic tests to obtain the right diagnosis. Conclusion: those rare cases need an optimum medical strategy to improve the capacity to establish an early positive diagnosis.

Key words: Prader Willi Like Syndrome, obesity, hyperphagia, chromosome 15, uniparentaldisomy

Introduction

PraderWilli syndrome (PWS) is a rare genetic disorder thateffects of 1:10,000 to 1:30,000 newborns, males and females, with no race particularities [1]. It is a multisystem disease with clinical, endocrine, metabolic and hormonal damage. It is the most common form of syndromic obesity. It is characterized by theclinical and genetic variability [2]. The clinical features are changing during life and they are influenced both age and early treatment. It is caused by a mutation of paternal copy of 15q11.2-13 region [3]. Approximately 70% of cases are determinate by a deletion of the specific region, 28% are due touniparentaldisomy (both copies of a chromosome were received from the mother), less than 1% of cases are caused by isolated mutations of the imprinting center with high risk of recurrence [4]. Some cases (1%) have an unknown cause; the patients have a positive clinical diagnosis of PWS, without the genetic confirmation (PWL syndrome).

To obtain a positive clinical diagnose of PWS, the clinical score established by Holm and collaborators is used. It involves major criteria noted with 1 point each one and minor criteria noted with 0.5 point each [5]. A clinical score of 5 points for children younger than 3 years (at least 3 major criteria present) and 8 for children over 3 years (5 points obtained from the major criteria) is required for a suggestive clinical diagnosis of PWS. There are also some supportive criteria (no point) who strengthen the clinical score (table 1).

The clinical diagnosis needs the molecular confirmation of chromosome 15 abnormalities to establish the positive diagnosis of PWS. PWL syndrome is a particular entity. It is caused by any mutations different by those who involved chromosome 15 but determine similar clinical features. The medical attitude for those rare cases is not fully elucidated.

Aim

The study aim is to present 6 patients with PWL syndrome and also to indicate a strategy to establish the right diagnosis for them.

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Table 1: Diagnosis criteria for PWS (Holm et al).

Major criteria (1 point each)	Minor criteria (1/2 point each)	Supportive criteria
Neonatal/infantile hypotonia and poor suck	Decreased fetal movement and infantile lethargy	High pain threshold.
Feeding problems and failure to thrive as infant	Typical behavior problems	Decreased vomiting
Weight gain at 1 to 6; obesity; hyperphagia	Sleep apnea	Temperature instability in infancy or altered temperature sensitivity in older children and adults
Characteristic dysmorphic facial features	Short stature for family by 15 years	Scoliosis or kyphosis (curvature of the spine).
Small genitalia; pubertal delay and insufficiency	Hypopigmentation	Scoliosis or kyphosis (curvature of the spine).
Developmental delay/ intellectual disability	Small hands and feet for height	Early adrenarche (pubic or axillary hair before age 8).
	Narrow hands, straight ulnar border	Osteoporosis (demineralization, or thinning, of the bones).
	Esotropia, myopia	Unusual skill with jigsaw puzzles
	Thick, viscous saliva	Normal neuromuscular studies
	Speech articulation defects	
	Skin peeking	

Material and Methods

We performed a retrospective study that analyzed data routinely collected as part of the clinical care of patients with PWL syndrome, derived from healthy non consanguineous parents. From the entire group of our department of PWS patients, we includedto study 6 patient, 3 girls and 3 boys, aged between 8 and 29 years old. All patients had positive clinical score for PWS and negative genetic tests (FISH test, methylation test) for the disease. We excluded all patients with positive molecular tests for PWS.We performed clinical examination and laboratory tests. We did not evaluate hypogonadism in 2 girls because of their small age.

The main phenotypic features were analyzed according to the international clinical diagnostic criteria for PWS (minor criteria and major criteria)[5]. The information about the pregnancy, postnatal evolution and the onset of hyperphagia and obesity were collected from interviews with the parents. We recorded their weight and height, we calculated the body mass index (BMI) and we compared the results with the standardized values for age and sex.

The laboratory tests included a complete evaluation of the carbohydrates, lipids and proteins metabolism and hormonal status (thyroid hormones, sex hormones, insulin).

Helped by a multidisciplinary team, we diagnosed the ocular abnormalities, the intellectual disabilities, developmental delay and language disorders. We also performed the necessary tests and interviews to identify supportive criteria- scoliosis or kyphosis, osteoporosis, early adrenarche, unusual skill with jigsaw puzzles.

The polysomnography was used to identify the sleep disorders (central, obstructive or mixed apnea). It was used a mobile device who monitors the brain function, the eye movements, the heart activity, ventilatory variables and arterial oxygen saturation during night sleep [6]. All parents were informed about the procedures, the risks and benefits of each tests and they signed informed consent.

Results

The mean age of all patients was 16.83± 8.47 years, for girls 13.33± 9.23 and for boys 20.33± 7.57. All of them had a positive clinical score for PWS, with a mean of 9±0.89 (Figure 1).

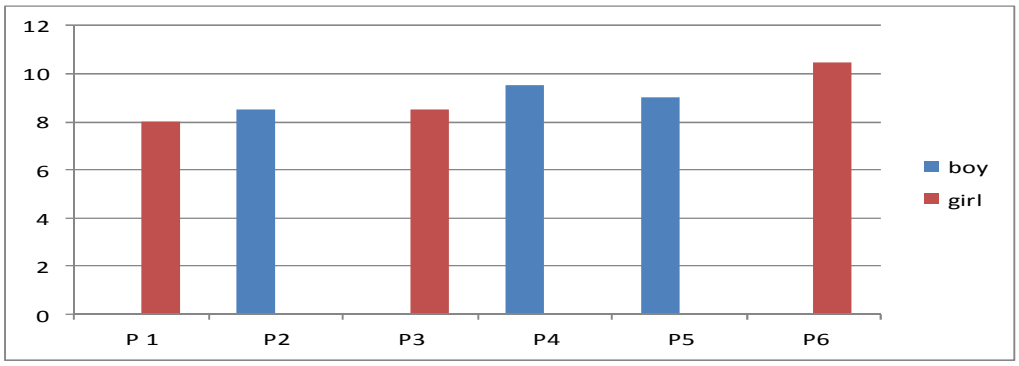

Figure 1. Clinical score distribution.

They all had more than 5 points obtained from the major criteria. The characteristic facial features were present at all 6 evaluated patients. They had narrow bifrontal diameter, almond shaped eyes, downturned corners of the mouth and small mouth with thin upper lip (figure 2).

Figure 2. PWL syndrome patients.

The patients had neonatal hypotonia according to parents' interviews. Feeding problems appeared in 66.67% of patients. They all were obese, with a weight gain before the age of 6 years based on hyperphagia. The onset of hyperphagia was different for each patient and the parents could not correlate it with a stressful event or other causes who could modify the feeding behavior of children. It is accompanied by aggressive reactions or excessive crying if they had no access to food. Hypogonadism appeared in 4 evaluated patients, 3 boys and 1 girl; they presented delayed gonadal maturation with delayed pubertal sign. All patients had moderate mental retardation and 3 of them needed special conditions for school (figure 3).

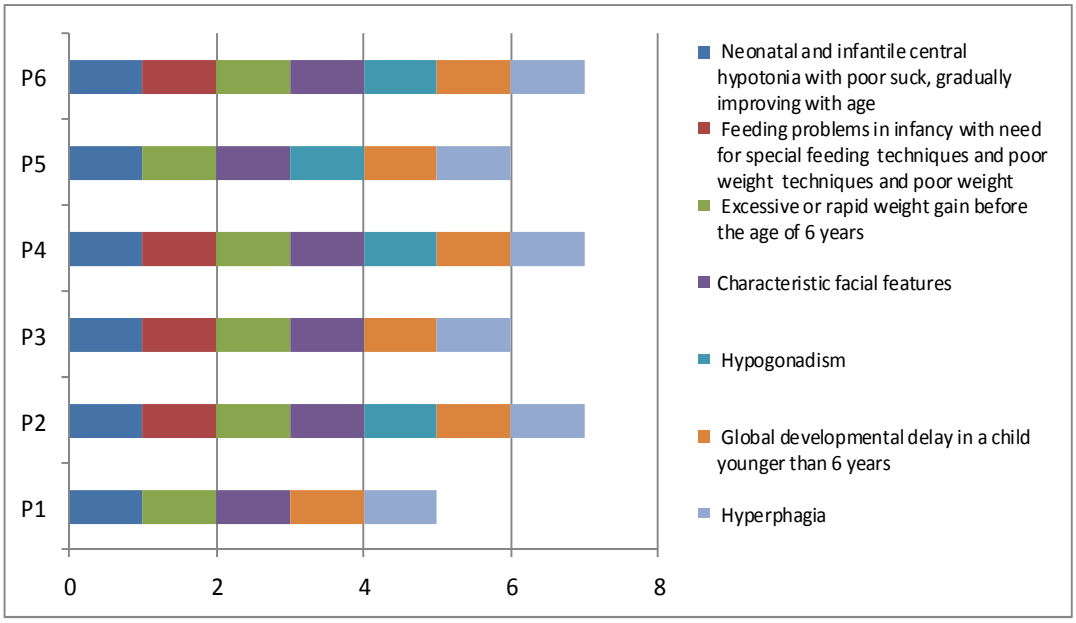

Figure 3: Major criteria distribution.

The minor criteria were also identified on patients. All of them had language difficulties with defects in words articulation and behavior problems. They presented aggressive, oppositional, manipulative and possessiveattitude, they were stealing (especially food) and they were lying. 83.3% of patients had sleep disorders. We diagnosed obstructive apneas, central and mixed apneas and hypopneas; patients associated restless sleep, oral breathing and increased sleepiness during the day and required specialized evaluation and treatment. Thick saliva had also a high frequency in our patients (83.3%); some of them presented crusting at corners of the mouth. Infantile lethargy with week cry was diagnosed in 66.67% of patients. We identified 3 patients (50%) with short stature according to the standardized values for age and sex. A small number of patients presented small hands and feet (16.67%) or ocular abnormalities.We did not identify osteoporosis or special skills with puzzles in our patients.

Discussions

The present study evaluated 6 patients with positive clinical diagnosis of PWS and without molecular confirmation. We searched the literature forsimilar cases to identify other gene mutation who can determine the same phenotype with PWS gene mutations. Izumi K et al in their paper from 2013 described the clinical and endocrine abnormalities in one patient with PWL syndrome associated with proximal interstitial 6q deletion involving Single-minded 1 (SIM1) gene [7]. They highlighted the clinical similarities between PWL syndrome and interstitial 6q deletion features and also the role of SIM 1 gene in the endocrine aspects and the importance of specific early treatment in the disease evolution.

Bonnefond et al presented the link between morbid obesity associated with PWL Syndrome and SIM1 loss of function [8]. They evaluated new mutations of SIM1 associated with chromosome 6q16 and their role in obesity from patients with PWL syndrome. Other studies who talked about the role of this gene in PWL syndrome were identified [9,10]. Those studies mentioned the 6q16 deletion as a critical mutation for PWL syndrome.

Pure distal monosomy 10q26 is mentioned in the literature as a specific mutation who determined similar clinical features with PWL syndrome. The symptoms of described patient had the onset in the prenatal period with decreased fetal movements. Other features of 10q26 monosomy are: severe neonatal hypotonia, characteristic facial dysmorphism, hypogenitalism and developmental retardation [11].

Schaaf et al described in their paper from 2013 4 different de novo heterozygous truncating mutations in the MAGEL2 gene [12]. They described 4 boys with PWL syndrome, two of them associated autism spectrum disorders or neurological problems like seizures.

Bischof et al. described the role of loss of MAGEL 2 gene in the hypothalamic dysfunction. They used an animal model who presented similar clinical features to PWS if they lose the expression of MAGEL2 gene [13].

All those studies highlighted the great genetic variability of PW phenotype; even if the disease is caused by a mutation of chromosome 15, there are also many other gene abnormalities who can determine the same clinical features.

Conclusions

Even if the medical knowledge in rare diseases area has been improved, there are still a lot of cases undiagnosed.The diagnosis of PWL syndrome follows the same steps like PWS diagnosis and the patients with PWL syndrome should be treated and evaluated like PWS patients till they get a complete gene evaluation and a positive diagnosis.We need to improve our capacity to investigate gene mutations, to search and to interpret them. More advance genetic tests (arrayCGH, clinical whole-exome sequencing) should be more accessible and should be used in case of an uncertain case. We also need center of expertise for PWS and with a larger study group we could try to identify some specific PWS phenotype features who allowed us to establish a diagnosis.A personalized early treatment and restrictive diet could increase the life expectancy and complications of morbid obesity, the main feature of PWL syndrome.

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