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Mini Review

Prader Willi Syndrome: Phenotypic and Genotypic Characteristics

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Abstract

Prader-Willi Syndrome (PWS) is a genetic disease caused by a lack of the fatherly PWS/AS region of chromosome 15. Its prevalence is estimated at 1 in 20,000 to 25,000 births.

We report the cases of 15 patients followed at the department of endocrinology. The diagnosis of PWS was based on clinical criteria of HOLMS and al and genetic study.

The sex ratio B/G was 8/7. Average age was 8.2 years (3-17).The reason for consultation was short stature: 2/3 associated with obesity 7/10. In other cases, children consulted for isolated obesity. Clinical presentation was typical in the majority of cases. All the major criteria for the diagnosis were found in patients with the exception of hypogonadism who was present in 2/3. Genetically, 8 patients have benefited from a genetic study. This was 2 Xq27-qter duplications, 5 deletions: 3p26.3 (n:1), 1p36 (n=1), p21.1 (n:1), q11.2 (n=2) of paternal chromosome 15 and one maternal disomy.

Therapeutically, institution of diet and lifestyle rules failed to reduce weight, but normalized the lipid and glucose balance. Treatment with metformin has been undertaken to improve insulin resistance.

GHr indicated in 8 cases has enhanced velocity of growth, achieve a significant height gain (+1,1 DS/MSempe; +1 DS/TC) and allow a slight reduction of overweight. The average weight reduction was 5 kg (2-7) after mean follow of 3 years.

Keywords: Prader-Willi Syndrome; Hypotonia; Obesity; Delay stature; Growth hormone

Introduction

Prader-Willi Syndrome (PWS) is a genetic disease caused by a lack of the fatherly PWS/AS region of chromosome 15 [1]. Its prevalence is estimated at 1 in 20,000 to 1 per 25,000 births. The annual incidence is estimated at 1 in 30,000 births [2].

It is characterized by a hypothalamic dysfunction associated with major hypotonia during the neonatal period and the first two years of life. From childhood to adulthood, the main problems are the appearance of a hyperphagia with morbid obesity, learning difficulties, behavioral problems and major psychiatric disorders [3].

The aim of the study was to report phenotypic characteristics of PWS children observed in our practice and identify the incriminated molecular abnormalities.

Population, methodology

15 patients with PWS were followed at the department of endocrinology. The diagnosis of PWS was based on clinical criteria of HOLMS and al [4] and on the genetic study. HOLMS and al Classification takes into account of the major and minor criteria. The points required for diagnosis of PWS syndrome are 4 points from the major criteria in children aged 3 years and under and 8 points in children older than 3 years with at least 5 points in the major criteria.

In addition to a complete physical examination and a psychological evaluation, all patients underwent a hypophysiogramme, cerebral MRI, metabolic balance cardiorespiratory exploration and Oto laryngoscopic examination. At the end of the exploration, blood samples were taken for genetic study of chromosome 15. Therapeutically, lifestyle and dietary rules were indicated in all patients as well as treatment with Growth Hormone (GHr) and insulin sensitizer drug (metformin).

Clinical Results

The sex ratio boys/girls are 8/7. The average age of the children was 8.2 years (3-17). The reason for consultation was motivated by short stature in 2/3 of cases associated with obesity seven times out of ten; in other cases, children consulted for isolated obesity (Table 1).

Clinical presentation was typical in the majority of cases. All the major criteria for the diagnosis were found in patients with the exception of hypogonadism who was present in two thirds of cases (Tables 2 and 3).

Obesity classified according to WHO curves [5] was present in all cases. It was severe in 86.6% of cases. These were the older patients (15 years and 17 years).

Paraclinical investigations showed complete growth hormone

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Table 1: Distribution of patients depending on the reason for consultation.

Reason for Consultation	Number	%
short stature	3	20
short stature and obesity	7	46.6
Obesity	5	33.3

Table 2: Major criteria of HOLMS and al [4].

Major Criteria	Number	%
Neonatal hypotonia	15	100
Rapid weight gain between 1 and 6 years, yperphagia	15	100
Swallowing difficulties at birth	15	100
Facial characteristics	15	100
Hypogonadism*	10	66.6
Learning disabilities, mental retardation	15	100

*Hypogonadism was constant among boys; it was noted in two girls in pubertal age (15 and 17 years old).

Table 3: Minor criteria of HOLMES and al [4].

Minor Criteria	Number	%
Decreased fetal movement, lethargy	6	40
Short stature	10	66.6
Acromicria	15	100
hypopigmentation	0	0
Behavior disorders	14	93.3
sleep disorders, apnea	5	33.3
Myopia	0	0
Strabismus	2	13.3
Dysarthria	1	6.66
Thick and viscous Saliva	1	6.66
Scratching of the skin	1	6.66

Table 4: Paraclinic results.

Exploration	Number	%
Hormonal balance		
-GH deficiency	15	100
-Average GH (mu/mL) before and after insulin test	0.22±0.3 ► 1.86±0.1	-
Gonadotropin deficiency		
-Boys	8/8	-
-Girls in pubertal age	2/7	-
-Thyreotropic deficiency	-	-
Doppler echocardiography		
-Abnormalities	-	-
-Without anomalies	13	100
Polysomnography and Oto laryngoscopic examination		
-Sleep apnea syndrome	3	23.07
-Metabolic balance	3	23.07
- Abnormal glucose tolerance	2	
-Diabetes mellitus	1	
-Hypertriglyceridemia	2	15.4
Testicular ultrasound		
-Bilateral cryptorchidism	8	100
Hypothalamic and pituitary MRI		
-Demyelinisation of sus tentorial white matter	4	26.6
- Normal pituitary	15	100

Table 5: Results of treatment with GHr.

Parameter	Before GHr	After GHr
Height (SDS/M, Sempe)	-2.5±0.4	- 1.4±0.1
Height (SDS/target height)	-2±0.1	-1±0.2

deficiency in all cases and gonadotropin deficiency among all boys and girls in pubertal age. It does not other endocrine insufficiency. The balance sheet found metabolic disturbances in a quarter of cases. We also noted sleep apnea syndrome once in four (Table 4).

The average height was -2.4±0.3 SDS (-2,-2.8)/Target height.

Genetically, 8 patients have benefited from a genetic study. This was two Xq27-qter duplications, five deletions: 3p26.3 (n:1), 1p36 (n=1), p21.1 (n:1), q11.2 (n=2) of paternal origin chromosome 15. In one case we found a maternal disomy (n:1).

Therapeutically, the institution of diet and lifestyle rules failed to reduce weight, but normalized the lipid and glucose balance. Treatment with metformin has been undertaken to improve insulin resistance that characterizes them.

Treatment with GHr was only possible in eight patients. In other cases, the treatment could not be instituted due to severe sleep apnea syndrome (Table 4).

GHr has enhanced the velocity of growth, achieve a significant height gain (Table 5) and allow a slight reduction of overweight. The average weight reduction was 5 kg (2-7) after mean follow of 3 years.

Discussion

PWS is a complex genetic disorder that is responsible for several clinical signs during childhood. It represents a major cause of mental retardation associated with a genetic disorder and is one of the main aetiologies of syndromic obesity.

The clinical diagnosis can be made according to the criteria defined by HOLMS in 1999 [4] Phenotypic presentation was typical in all cases (Tables 2 and 3).

Hypotonia at birth is a constant sign. It is accompanied by a hard suction. Developmental delay is also a constant sign and walking is delayed [6].

Hypogonadism is evident at birth especially among boys. It causes a micropenis and cryptorchidism. This deficiency of central origin is responsible for delayed puberty and infertility.

The learning disability becomes evident at school. Mental retardation is mild to moderate and learning disability is not correlated with mental retardation.

Towards the first year, hyperphagia appears, resulting in a very significant weight gain with a compulsion to satisfy its food needs [6].

The early onset of severe obesity explains of the morbidity and mortality of these patients. Various complications can occur: diabetes mellitus, dyslipidemia, cardiovascular and respiratory complications.

The constant search for food is probably due to a lack of regulation of complex system of satiety, actually not known precisely. High levels (3 times normal) of ghrelin, an hormone secreted by the stomach, whose role is to control both food intake and growth hormone secretion, exist in these patients regardless of age and corpulence. Unlike lowered rates are found in common obesity or other genetic obesity (leptin deficiency, mutations of MC4R gene). The pathophysiologic mechanism is not understood. Indeed, the decrease of ghrelin levels by somatostatin did not result in significant changes of feeding behavior [7].

Other endocrine abnormalities related with still hypothalamohypophysaires abnormalities are found. Other endocrine abnormalities related with still hypothalamohypophysaires abnormalities are found. They associate short stature due to growth hormone deficiency found in 50-100% of cases [8] and incomplete pubertal development in relation to a partial hypogonadism. It was reported deficient neurons secreting oxytocin. There are also other finer hormonal damage as pubarche premature and hypothroïdie found in about 30% of cases [9].

Delay stature appears after the 1st year of life, between 3 and 10 years; Growth has averaged about -2 SDS (*Versus*-2.5 SDS in our patients). The peak pubertal growth is reduced resulting in adult height that is on average 162 cm for men and 150 cm for women. Hypogonadism is confirmed at puberty. While cases of complete puberty have been reported, usually pubertal development is delayed and incomplete.

Several studies have shown that treatment with GH replacement doses prescribed as the usual replacement dose has stature acceleration. When the treatment started before the age of puberty, it causes normalization of the size and a height gain of 1.8 SDS after 4 years of treatment [10]. It improves body composition with a decrease in fat mass of 8 to 25% according to the authors is also noted; this effect occurs mainly the first year [11].

In the PWS, energy expenditure is decreased and significantly increased under treatment with increasing fat utilization. We also see an increase in agility and muscle performance.

Increased respiratory capacity partly related to the effect of GH respiratory muscles was observed too. Because of the dramatic effects, GH treatment is indicated in the PWS, of whether there is or not GH deficiency.

Indeed, the growth hormone treatment is indicated either correct delay stature or to its metabolic effects (decreased fat mass). It represents the first metabolic indication of growth hormone in children.

During treatment with GH glucidic balance must be particularly monitored.

GH treatment causes insulin resistance. Or Children with PWS have a higher risk of developing diabetes type 2 probably due to their overweight.

Studies have shown an increase of plasma insulin with GHr but glucose tolerance remains normal. So it is recommended to evaluate glucose tolerance before beginning treatment and subsequent monitoring especially if overweight. In case of preexisting scoliosis, an aggravation can be dreaded because of the growth spurt triggered by GHr. A closer orthopedic monitoring is necessary.

GH treatment should be started after removing all causes of nasal obstruction by a specific examination and also after verifying the absence of central apnea by polysomnography. Indeed rare cases of death from respiratory abnormalities have been described in children with PWS, treated or not with GH [12].

It is possible that in these children having narrower nasal, GH is a precipitating factor breathing difficulties by hypertrophy of lymphoid tissue that it may induce.

This important risk prevented us prescribe the GHR in three of our patients because of severe sleep apnea syndrome.

Psychological behavior characteristic of this syndrome appears early: Obsessive-compulsive disorder, tantrums, obstinacy fear of change [5].

Psychotic forms, however, are extremely common in adult patients with maternal disomy (our patient) and are not described in others [13].

Genetically SPW is a pattern of genomic imprinting involving microRNAs nucleolar. It is a contiguous gene syndrome, linked to the 15q11-q13 chromosome region [14].

While most genes are active or inactive similarly for the two copies, some require that one of the parental copies is suppressed. This gene repression is called genomic imprinting [15]. It is the epigenetic phenomenon by which certain genes are expressed in a parent-of-origin-specific manner. If the allele inherited from the father is imprinted, it is thereby silenced and only the allele from the mother is expressed. If the allele from the mother is imprinted, then only the allele from the father is expressed. Appropriate imprinting of certain genes is important for normal development. Human diseases involving genomic imprinting include PWS.

It is the absence of the region of PWS/AS paternal chromosome 15 which is the cause of this pathology. Several mechanisms are responsible for the lack of PWS/AS region. In 70% of cases, there is a deletion of the q11.2-q13 locus of chromosome 15. This deletion concerns only the paternal chromosome. In 25% of cases there is a maternal disomy of chromosome 15. The absence of the paternal chromosome 15 prevents the expression of the PWS/AS region. In 5% of cases, it is a default of expression.

Of the PWS/AS region which is nevertheless present. In general, It is a microdeletion undetectable by cytogenetic [14,16,17].

These proportions of molecular abnormalities have been observed in our patients despite the genetic study was not performed in all cases.

Most cases of PW are not hereditary. In particular, those related to a deletion of 15 or paternal chromosome disomy of maternal origin [14].

These genetic exchange as random events occur during the formation of reproductive cells or in early embryonic development. Rarely, a genetic change responsible for Prader-Willi Syndrome can be inherited. For example, it is feasible for a genetic exchange that abnormally inactivates genes on the paternal chromosome 15 to be passed from one generation to the next [14].

There is no strict consensus today on the existence of genotypephenotype correlation but there are data for some phenotypic characteristics that evoke a strong relationship with the genotype. The global cognitive efficiency would be the same level regardless of the genetic form. The verbal skills of individuals with disomy are better than those of deleted subjects but there are differences regarding non-verbal skills [18,19].

Studies, involving adolescents and young adults with PWS, showed phenotypic differences according to the type of deletion (long 1 or 2 short form) [20]. The distinctions found between these three genetic types-both deletions and disomies-relate to behavioral problems (mainly the presence of adaptive behavior), psychological (the intensity of the obsessions and compulsions) and cognitive (visual-integration processes driving, performance in reading and mathematics). Thus, subjects with the most extensive deletions (subgroup 1) a significantly greater and more compulsive behavior altered visual perception. Patients with shorter deletions (subgroup 2) would present nearest phenotypes from those described in the maternal uniparental disomies group [21,22].

There is extreme variability of psychiatric clinical features; however, adult patients with maternal disomy, psychotic crisis are extremely common, which is not found in patients with a deletion [13].

An early global and multidisciplinary care, associated with growth hormone treatment for optimum effect is essential: dietary monitoring, physiotherapy, regular practice of a sport and physical activity, psychological and/or psychiatric care.

Early diagnosis and management are recognized as important elements. They are in principle associated with better development of children, especially in terms of weight.

Conclusion

Early diagnosis confirmed by genetic study associated with a multidisciplinary approach improves the functional and vital prognosis of PWS patients and to provide them a better quality of life. However, the constant and long-term need for food restriction, behavior management and medical care May be hard for PWS patients and family members. They must be accompanied and supported.

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