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Original article

Prader-Willi Syndrome: an under-recognized cause of hypotonia?

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Abstract

The "floppy infant" is a well-recognized entity characterized by generalized hypotonia presenting at birth or in early life. Hypotonia represents a diagnostic challenge because it may be the presentation sign of numerous diseases, as central or peripheral nervous system abnormalities, myopathies, genetic disorders, endocrinopathies, metabolic diseases and acute/chronic illness. Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder that results from an abnormality in chromosome 15. Diagnosis is often delayed because clinical findings are relatively nonspecific and the dysmorphism is often subtle.

We describe three term male newborns admitted in the first day of life for hypotonia and feeding difficulties. Pregnancy and familiar history were unremarkable. Clinical examination revealed marked global hypotonia, few active movements, weak cry, poor suck reflex, micrognathia, cryptorchidism, facial dysmorphic features: almond-shaped eyes with short palpebral fissures, narrow bifrontal diameter and short neck. Laboratory evaluations were normal. Brain ultrasound and magnetic resonance had no alterations. Cardiac and metabolic evaluations were irrelevant. PWS was suspected and genetic evaluation was performed. The methylation analysis specific for PWS confirmed the diagnosis. In the three cases it was observed development milestones delay, with progressive improvement after multidisciplinary approach. At last follow-up visit, all of them walk alone, explore the surrounding environment, understand simple language and say some words.

These reports reinforce the idea that PWS should be considered in the presence of newborn hypotonia, and feeding difficulties, even in absence of typical facial features. Detecting PWS at neonatal age is important because it allows early intervention and better management of such infants.

Keywords

Cryptorchidism, facial dysmorphisms, feeding difficulties, genetic disorder, neonatal hypotonia, Prader-Willi Syndrome.

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Introduction

The "floppy infant" is a well-recognized entity characterized by generalized hypotonia presented at birth or early in life. Hypotonia itself represents a diagnostic challenge for pediatricians because it may be the presentation sign of numerous diseases as central or peripheral nervous system abnormalities, myopathies, genetic disorders, endocrinopathies, metabolic disorders and acute or chronic illness [1, 2]. Prader-Willi Syndrome (PWS) is frequent among infants with hypotonia and it should be considered by pediatricians and neonatologists in the differential diagnosis of all hypotonic newborns [3]. A systematic approach to a child who has hypotonia, paying attention to the history and clinical examination, is essential for a correct diagnosis.

PWS is a rare complex multisystem genetic disorder involving genomic imprinting, and is caused by the lack of expression of paternally inherited genes in the PWS region of chromosome 15 (15q11-q13). Its prevalence is estimated at 1 in 20,000 to 1 in 25,000 births. The annual incidence is estimated at 1 in 30,000 births [4-9]. Clinical diagnosis criteria of PWS were initially proposed by Holms in 1981, and a consensus was published in 1993 [10]. Actually, the definitive diagnosis is genetic, based primarily on the DNA methylation analysis, followed by chromosomal analysis with Fluorescence *In-Situ* Hybridization (FISH) that identifies cases due to deletion of chromosome 15. If the FISH does not highlight any deletion, it is necessary to use a Methylation Polymerase Chain Reaction (PCR) microsatellite analysis that will allow to highlight a uniparental disomy or an imprinting center mutation. Although the definitive diagnosis is genetic, clinical findings continues to be essential to diagnosis suspicion, and the cardinal features of PWS include neonatal hypotonia and feeding difficulties, dysmorphic features, short stature, hypogonadism, cognitive impairment and hyperphagia with subsequent obesity [4, 6-8, 11]. Hypotonia has a prenatal onset and is a nearly universal finding that is usually manifested as decreased fetal movements, abnormal fetal position at delivery and increased incidence of assisted delivery or cesarean section, associated with a tendency for intrauterine growth retardation. Due to the marked hypotonia, many of them experienced birth asphyxia and consequently increased use of resuscitation in the delivery room. At infancy, they manifest weak cry, lethargy and poor reflexes, including poor suck. The hypotonia usually improves over the time but mild-to-moderate hypotonia may persist throughout life. In both sexes, hypogonadism manifests as genital hypoplasia, incomplete pubertal development and infertility in the vast majority. In males unilateral or bilateral cryptorchidism is present in 80-90% of the cases and it is strongly indicative of PWS. It is also known that PWS patients have abnormal temperature regulation, particularly hypothermia, probably a manifestation of hypothalamic dysfunction, and may be predisposed to hypoglycemia from birth although additional investigation is necessary to define the cause of hypoglycemia [9, 12].

In newborns, PWS is quite difficult to diagnose, as it differs from that seen later and the dysmorphic features may not always be present.

Case reports

We report three term male newborns admitted to our Neonatal Intensive Care Unit on the first day of life for hypotonia and feeding difficulties. Pregnancy and familiar history were unremarkable and there was no consanguinity. In one case there was intrauterine growth restriction but no one was born prematurely (**Tab. 1**).

Clinical examination revealed marked global hypotonia, few active movements, weak cry, poor suck reflex, micrognathia, cryptorchidism and some facial dysmorphic features: almond-shaped eyes with short palpebral fissures, narrow bifrontal diameter and short neck (**Tab. 2**, **Figures 1-3**).

Laboratory evaluations, including blood glucose assay, urine analysis, electrolytes, blood count, infection markers, renal, hepatic and thyroid function were normal. Brain ultrasound (performed in 3 out of 3 cases) and magnetic

Table 1. Perinatal clinical characteristics.

	Case 1	Case 2	Case 3
Date of birth	2014	2015	2015
Gender	Male	Male	Male
Father/mother age	29/30	33/37	28/30
Pregnancy and delivery	Term, cesarean	Term, cesarean	Term, vacuum
Percentile birth weight	P3-15	P50	P15-50
Percentile birth length	< P3	P50	P15-50

Table 2. Phenotypic characteristics.

	Case 1	Case 2	Case 3
Hypotonia	+	+	+
Feeding difficulties	+	+	+
Typical craniofacial features [a]	+	+	+
Hypogenitalism	Hypoplastic scrotum cryptorchidism	Hypoplastic scrotum cryptorchidism	Hypoplastic scrotum cryptorchidism
Small hands and feet	-	-	-

[a] Almond-shaped eyes with short palpebral fissures, narrow bifrontal diameter and short neck.

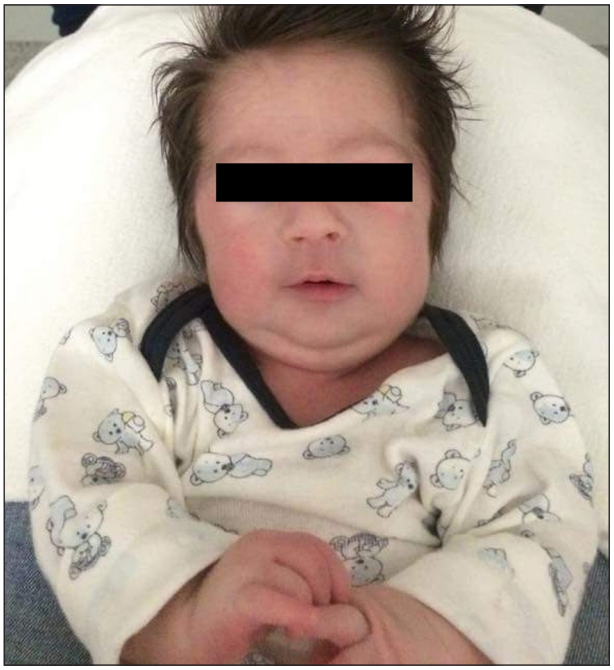

Figure 1. Craniofacial features (frontal view) of the newborn described in case 3.

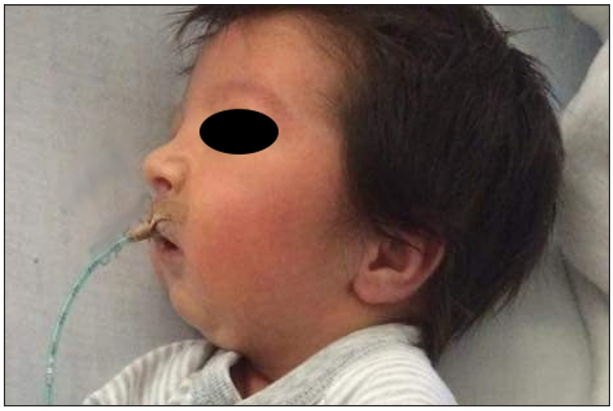

Figure 2. Craniofacial features (left profile) of the newborn described in case 3.

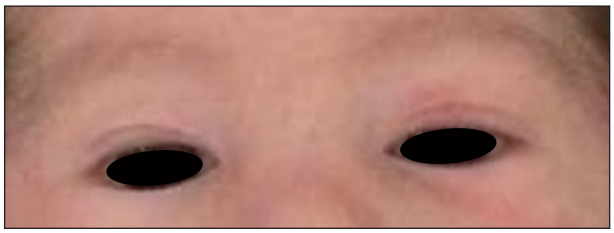

Figure 3. Almond-shaped eyes with short palpebral fissures of the newborn described in case 3.

resonance (performed in 2 cases) had no alterations. Cardiac and metabolic evaluations were irrelevant. PWS was suspected and genetic evaluation was performed. The methylation analysis specific for PWS confirmed the diagnosis. The genetic alteration identified, in the three cases, was 15q11-q13 microdelection (**Tab. 3**).

These infants received a multidisciplinary approach, presenting progressive improvement of hypotonia and feeding difficulties after physiotherapy treatments. At last follow-up visit, with 30, 24 and 20 months, respectively, all of them had recovered the feeding difficulties and the two older boys were at hyperphagic phase, with an increasing in weight percentile. Although they had development milestones delay and maintain some global hypotonia, actually they walk alone,

Table 3. Complementary diagnostic study.

	Case 1	Case 2	Case 3
Analytical study	N	N	N
Brain ultrasound	N	N	N
Brain magnetic resonance	-	N	N
Echocardiogram	-	Patent ductus arteriosus	Patent foramen ovale
Abdominal and pelvic ultrasound	N	N	N
Metabolic study	N	N	N
Clinical genetic evaluation	PWS suspicion	PWS suspicion	PWS suspicion
Laboratorial genetic evaluation	46, XY Deletion 15q11-q13	46, XY Deletion 15q11-q13	46, XY Deletion 15q11-q13

N: normal; PWS: Prader-Willi Syndrome.

Table 4. Anthropometric and developmental characteristics.

	Case 1	Case 2	Case 3
Anthropometric parameters (last follow-up)	Weight P50 Length P3-15 (30 months)	Weight P50-85 Length P50 (24 months)	Weight P3-15 Length P3-15 (20 months)
Psychomotor development (last follow-up)	< age group (30 months)	< age group (24 months)	< age group (20 months)
Cephalic control	4-5 months	4 months	4 months
Axial control	11-12 months	7 months	7 months
First words	14-15 months	15 months	18 months
Walk alone	30 months	18 months	18 months

explore the surrounding environment, understand simple language and say some words (**Tab. 4**).

Discussion

PWS is a complex multisystem genetic disorder characterized by hypothalamic-pituitary dysfunction. Diagnosis is often delayed because clinical findings are relatively nonspecific and the dysmorphism is often subtle. In our hospital during a period of five years (2012-2016), 13,807 births occurred and 9 of them had PWS diagnosis, but only the 3 reports we presented were diagnosed in the neonatal period. The prevalence of PWS in our institution (13:20,000 births) was higher than it was described in the literature; so, we hypothesize that PWS can be more frequent than it is reported, as it is also mentioned by some other authors [4, 13].

There is published consensus of clinical criteria for PWS diagnosis but genetic testing has become the standard [4-9]. All children we presented were diagnosed early, although the diagnostic doubts led to metabolic and imaging studies in all of them. Thinking about this syndrome in the differential diagnosis of hypotonic newborn can prevent the realization of invasive complementary exams, sometimes difficult to interpret, and allow an early intervention which can favorably influence the evolution of the disease.

Concerning the neonatal period, central hypotonia with poor sucking, feeding problems with need for special feeding techniques, hypogonadism and characteristic facial features such as dolichocephaly, almond-shaped eyes, thin upper lip, and narrow bifrontal diameter are the most clinically relevant criteria for detecting PWS. Although in the cases we reported hypoglycemia was not present, infants with PWS may also be predisposed to hypoglycemia from birth, so glucose monitoring and surveillance is necessary. Early detection and treatment of hypoglycemia may result in improved neurocognitive outcomes for these patients [12].

PWS results from genetic alterations at chromosome 15 inherited from the father. Three main molecular mechanisms are responsible for PWS manifestations: paternal deletion, maternal uniparental disomy (two copies of this chromosomal region from the mother) and imprinting defects. So, if PWS is suspected, DNA methylation studies specific for PWS should be ordered to confirm the diagnosis [4-9, 11]. Genetic

counseling often is helpful for parents of a child affected with PWS who are contemplating another pregnancy. The risk of recurrence varies widely (zero to 50 percent) depending on the underlying genetic origin and can be determined based on the results of genetic testing [4-9].

The clinical course of PWS has historically been divided into two distinct clinical stages (early failure-to-thrive and later childhood obesity). Hypotonia at birth is a common sign and it is accompanied by weak suction. Hypogonadism is evident especially among boys, and it causes a micropenis and cryptorchidism. This deficiency of central origin is responsible for delayed puberty and infertility. Development milestones delay is also a frequent sign and learning disability becomes evident at school. Mental retardation is mild to moderate but 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. Various complications can occur: diabetes mellitus, dyslipidemia, cardiovascular and respiratory complications, but the early onset of severe obesity explains the morbidity and mortality of these patients. So, prevention of obesity is one of the most important aspect to promote among patients and their families [4-9, 11]. Parents should be informed that eating difficulties improve progressively but the weight gain from the second year of life is very difficult to control.

Treatment of a child with PWS involves a multidisciplinary team with early global intervention: supplemental tube feedings to avoid failure to thrive in the first year of life, ophthalmologic evaluation due to the risk of myopia and strabismus, endocrinologic evaluation for consideration of growth hormone treatment, treatment of hypoventilation problems, psychomotor development monitoring with early intervention for motor skills, speech and language as an individual educational plan. Generally, after the first year of life, strict dietary supervision and physical activity plans should be initiated to reduce cardiovascular and respiratory disorders that are the leading causes of death [4-9, 11].

Conclusions

PWS should be considered in the presence of newborn hypotonia and feeding difficulties, even in absence of other characteristics. Detecting PWS at neonatal age is important because it allows early intervention with a multidisciplinary approach to provide better prognosis and quality of life.

Declaration of interest

The Authors declare that there is no conflict of interest.

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