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Prader-willi syndrome: importance of early diagnosis - case report

Síndrome de prader-willi: importância do diagnóstico precoce – relato de caso

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ABSTRACT
Prader Willi Syndrome is a genetic disease caused by the lack of expression of genes on chromosome 15 (chromosomal region 15q11-q13). In 1956 it was described for the first time by Prader, Labhart and Willi. It is a complex neurodevelopmental disorder, regardless of ethnicity or sex. The main features of the syndrome in the neonate are hypotonia, hypogonadism, difficulty in sucking the breast and facial dysmorphisms. PWS has two different clinical nutritional phases. The first begins at birth, characterized by difficulties in latching on to the breast due to low suction. In the second phase, from the age of 2, the child has excessive hunger that leads to progressive obesity, if not controlled by the diet. The diagnosis of PWS is made by non-invasive genetic testing. DNA methylation analysis detects the condition more than 99% of the time and is therefore considered the first-line genetic test. This study aimed to analyze the importance of early diagnosis in the pediatric population, based on a case report that occurred in a maternity hospital in the Planalto Norte Catarinense. The study was qualitative in nature with a descriptive and retrospective orientation. Data collection was performed from the patient's chart. In the development of this analysis, the importance of early diagnosis for rapid intervention and improvement of prognosis and quality of life of these patients became evident. Early diagnosis and appropriate care are crucial for the baby's outcome, as it ensures comprehensive care to prevent obesity and stimulation of cognitive and adaptive skills.

Key-words: Prader-Willi syndrome, Early diagnosis, Clinical manifestations, Clinical management, Deletion 15q11q13.

1 INTRODUCTION

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder caused by the lack of gene expression in the region of chromosome 15q11-q13 inherited from the father (ANGULO; BUTLER; CATALETTO, 2015). "PWS was the first recognized human disorder related to genomic imprinting and the first that was shown to be caused by uniparental disomy" (CASSIDY; DRISCOLL, 2008, p. 3).

First described in 1956 by Prader, Labhart and Willi, Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder with no distinction of ethnicity or social status association (DIMITROPOULOS, 2010). It is estimated that there are 400,000 cases of the syndrome worldwide. The pathology affects both sexes equally. The incidence of the disease is 1 in 25,000 newborns. Most cases are sporadic and familial recurrence is infrequent (TRAVIESO TELLEZ; MENENDEZ GARCIA; LICOURT OTERO, 2014).

At gestational stage, the fetus is within normal growth patterns, but have decreased fetal movements due to prenatal hypotonia. They usually require cesarean section or assisted delivery due to abnormal fetal position at the time of delivery (MILLER et al., 2011).

In the neonatal period, infant hypotonia is a frequently observed finding, with weak crying, decreased movements and reflexes. The hypotonia is of central origin. They also present with low

sucking and lethargy. During infancy, most children have delayed motor and growth development. Language is affected by apraxia and difficulties in articulating sentences. Intellectual delay is noticed when the child reaches school age (MILLER, 2012).

Cheon (2016), points out that Prader Willi Syndrome has 2 different nutritional clinical phases. The first one begins at birth, characterized by difficulties in breastfeeding due to low suction. In the second phase, starting at 2 years of age, the child with the syndrome has excessive hunger that leads to progressive obesity if feeding is not controlled.

Other characteristics of these patients are the easy typical of the syndrome (they have craniofacial dysmorphy, dolichocephaly, almond eyes, downward lip commissures and strabismus), in addition to small hands and feet (BEXIGA et al., 2014, p. 30). They present genital alterations with cryptorchidism, and hypogonadism in males and hypoplasia of the genital organs in females. Several behavioral changes from childhood to adulthood affect these patients, from anger crises, attention deficit, obsessive-compulsive behavior, and binge eating (ANGULO; BUTLER; CATALETTO, 2015).

Heksch et al. (2017), writes about the range of pathologies that patients with PWS develop. The hypothalamic dysfunction generated by the syndrome, leads to endocrinopathies such as GH (growth hormone) deficiency, hypogonadism, hypothyroidism, adrenal insufficiency, and low bone density. In addition to hypothalamic dysfunction and lack of satiety, individuals with PWS have lower resting energy expenditure, increasing the risk of obesity that can be complicated by metabolic syndrome and type 2 diabetes mellitus.

The most serious complication of the syndrome is obesity caused by binge eating and low energy expenditure. Obesity leads to insulin resistance, cardiovascular and respiratory diseases that decrease the life expectancy of these patients (KUO et al., 2007). According to the Brazilian Society of Pediatrics (2017), when patients are evaluated, it is difficult to differentiate which deleterious effects were caused by the syndrome itself and which were caused by obesity.

According to Setti et al. (2012), it was observed that a large portion of the deleterious effects of PWS can be mitigated with correct diagnosis and early therapeutic interventions. It is very important to have an integrated multidisciplinary team and to develop care protocols for the management of patients with Prader-Willi Syndrome.

In the absence of early diagnosis and treatment, the patient develops excessive weight gain, leading to severe early obesity between 3 and 4 years of age. Clinical suspicion is possible in the first months of life, as these infants have severe hypotonia, signaling the need for a genetic study (BAR *et al.,* 2017).

There are different methods to confirm the diagnosis and identify the genetic subtype. DNA methylation analysis should be the test of choice for initial investigation, as it has the highest sensitivity and specificity. If this test shows only a maternal pattern, then PWS is confirmed (GOLDSTONE *et al.*, 2008).

Given these data, it is possible to analyze that it is of great relevance in the medical field, specifically in the pediatric area, that the early diagnosis of PWS brings an improvement in the quality of life of carriers of the disease.

For this reason, the present article aims to analyze the importance of early diagnosis in patients with Prader Willi Syndrome, based on a case report from a maternity hospital in Planalto Norte Catarinense, taking into account that this action is fundamental to improve the quality of life and favorable prognosis of a newborn.

It is worth pointing out that PWS has no cure, but early diagnosis in the first months of life is of utmost importance, so that treatment and follow-up can be started as soon as possible. If followed correctly and controlling the comorbidities, the syndrome carriers can have much higher quality and life expectancy.

2 MATERIAL AND METHODS

This is a qualitative study with descriptive and retrospective orientation, based on an analysis of the importance of early diagnosis in a newborn assisted in a maternity hospital in Santa Catarina. Data collection was performed from the patient's medical records during the period of hospitalization.

Before collection, the authorization and commitment term for the use of information was sent to the director of the maternity hospital to implement the research on the premises of the institution and collect data from medical records. The maternity was assured that data collection occurred without interfering in the routine of the professionals and ensuring safety measures against contamination by Covid-19, i.e., use of PPE by the researcher and respect for the necessary distance.

The confidentiality of the data obtained was guaranteed and ensured. The variables investigated from the medical records were related to the main information regarding the patient's evolution, including: date of birth, admission date, birth weight, gestational age, clinical profile, procedures performed, medications administered, test results, length of stay, and outcome.

The sampling was obtained from the analysis of the medical record of the patient who was admitted to the maternity hospital in the year 2021 diagnosed with PWS, as well as from the author's analysis during a visit to the patient at 10 months of age.

This study considered as inclusion criteria: newborns diagnosed with Prader-willi Syndrome in the year 2021, in a maternity hospital in Planalto Norte Catarinense.

The research project was submitted to the Research Ethics Committee of the Universidade do Contestado and approved under opinion number 5.388.476 and CAAE 58050122.8.0000.0117.

3 CASE REPORT

CFS, newborn, female, was born with a gestational age of 38 weeks and 1 day, weighed 2735g, and was classified as SGA (small for gestational age) APGAR 7/8, and did not require resuscitation maneuvers. His birth occurred in a maternity hospital in the interior of Santa Catarina in the second semester of 2021.

A 41-year-old mother, her gestational history included: 4 pregnancies, 2 normal deliveries, 1 cesarean section and 1 abortion (G4XP2XC1XA1); she had 10 prenatal visits, blood type AB positive. She had all negative serologies, and had immune toxoplasmosis serology. There is no report of previous diseases important to the case. During gestation, she presented bleeding and DHEG (gestational hypertensive disease). Quarterly morphological USG (ultrasound) and nuchal translucency normal. No other complications until 38 weeks, when she arrived at the maternity hospital, was diagnosed with ruptured bag and referred for cesarean section.

Father, 31 years old, apparently healthy and with no relevant personal history. No history of consanguinity.

On first physical examination, the newborn presented with stable vital signs, ruddy and anicteric with weak and feeble crying. Hippoactivity and wrists in flexion, protruding calcaneus, blotchy feet, slightly rotated ears with alteration in curvature, retrognathia, ogival palate and hypertrophy of the gums. On cardiac auscultation, normal rhythmic heart sounds, without murmurs. Pulmonary auscultation revealed a symmetrical vesicular murmur. Flaccid abdomen without visceromegaly. Typically female genitalia, Ortolani was negative, palpable peripheral pulses. Primary reflexes were present but slightly diminished.

Mother and daughter were referred to the room, where she presented difficulty in breastfeeding, hypotonia, tachypnea, and acrocyanosis, and was referred to the ICU for investigation, follow-up, and feeding therapy, where a nasogastric tube was indicated. The next morning, she evolved with progressive respiratory worsening, being tachypnea and with signs of

respiratory distress (retraction of the sternal furcula), requiring inhaled oxygen therapy with good response.

As for the exams performed during the ICU admission, the RN had normal blood count, except for the elevated CRP. Liquor without alterations. Chest X-ray without abnormalities Abdominal USG and echocardiography without alterations.

On the ninth day, the results of the heel prick are normal. As the tests performed so far were considered normal, the team discusses the referral of the case for investigation by a pediatric neurologist and geneticist, and a karyotype is requested.

At 16 days of life, a nasoenteric tube is indicated because the patient has feeding difficulties characterized by vomiting, sucking disturbance, and insufficient weight gain (she is at 2780g). On the 21st day she is discharged to the rooming-in unit, still waiting for the karyotype results, and consultations with a specialist.

In consultation with the neuropediatrician, the family was informed that the hypotonia and low suction would not be linked to central pathologies, and should research genetic syndromes.

At 30 days of life, still hospitalized in the rooming house, hypotonia remains, weak crying, interspersing long periods of sleepiness with periods of alertness. She continues on a tube diet, with good acceptance.

On the 40th day, he received the karyotype result as normal, while he awaits a consultation with the geneticist to decide on the next steps to be taken. During this period, she gained weight, receiving a diet via tube and also by bottle. At 50 days, the nasoenteric tube was removed, since he was accepting 70 ml orally 3/3 hours.

In consultation with the geneticist, a PCR-methylation test was requested, and the result was a deletion, uniparental disomy, or imprinting mutation in the SNRPN gene on the paternal allele, diagnosing the patient with Prader-Willi Syndrome.

In the evolution, she was discharged from the maternity ward with improvement of the feeding difficulties and improvement of the hypoactivity. The mother participated actively in the follow-up and stimulation of her daughter together with the team.

4 DISCUSSION

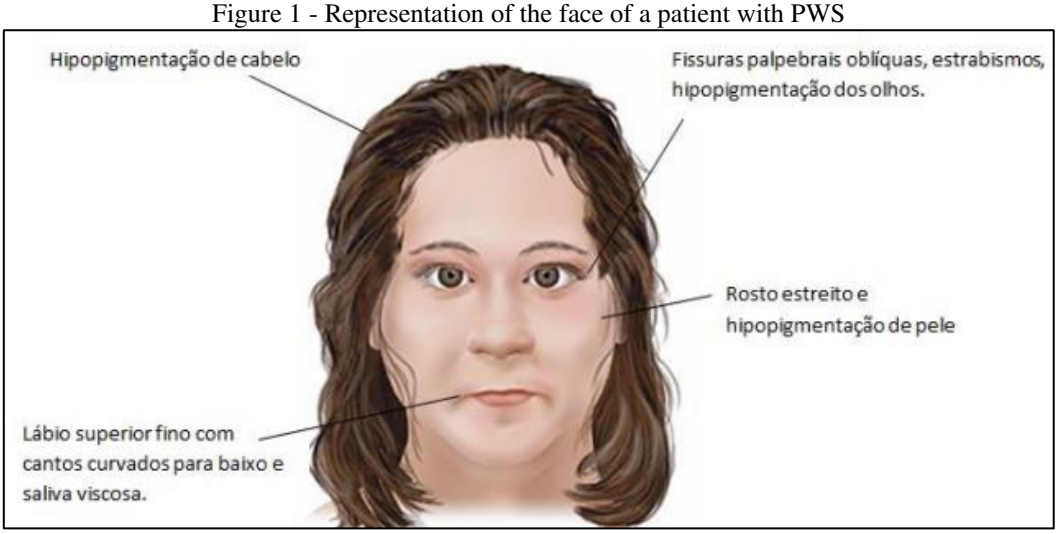
4.1 MAIN CLINICAL MANIFESTATIONS

The characteristics of PWS are already evident at the birth of the baby, as these present with infant hypotonia, weak and feeble crying, difficulty in breastfeeding, as well as hypogonadism with hypoplastic clitoris and labia in girls and a small penis with cryptorchidism in

boys (BUTLER; MILLER; FORSTER, 2019). During gestation, mothers may report decreased fetal activity and babies are often found in the breech position at the time of delivery (CATALETTO et al., 2011).

In addition, they have typical facial features such as narrow bifrontal diameter, strabismus, almond-shaped palpebral fissures, hair hypopigmentation, low nasal bridge, and thin upper lip with downward curved corners (Figure 1). These traits may or may not be present at birth, but will develop during the child's life (CASSIDY et al., 2012).

Figure 1 - Representation of the face of a patient with PWS



Source: Dianesi (2018)

The patient described in the clinical case presented the general characteristics of Prader-Willi Syndrome referred to in the literature, such as: hypotonia at birth, difficulty in breastfeeding, weak and feeble crying, small hands and feet. Typical facial features included hypopigmentation of hair, strabismus, light eyes, oblique palpebral fissures, and downward curved lips. In addition, the patient presented short stature and weight for age.

According to Bexiga et al. (2014), the most prevalent changes at birth and early childhood are hypotonia, difficulty sucking and craniofacial dysmorphism, hypogonadism, and small hands and feet. Hypotonia tends to improve between 8 and 11 months, but psychomotor developmental delay worsens from 2 years of age. Hyperphagia (94%) and short stature (76%) are late signs of PWS, but can be controlled and remedied by early treatment with a multidisciplinary team.

Cheon (2016), points out that Prader Willi Syndrome has 2 different nutritional clinical phases. The first one begins at birth, characterized by difficulties in breastfeeding due to low suction. In the second phase, starting at 2 years of age, the child with the syndrome has excessive hunger that leads to progressive obesity if feeding is not controlled.

In early childhood, delays in motor and language development are observed, with milestones usually reached at twice the normal age. Intellectual and learning disabilities are usually seen in the school stage (PASSONE et al., 2018).

According to the Brazilian Prader Willi Syndrome Society, developmental delay is always noted, varying in severity from patient to patient. On its website there is a guide showing the developmental milestones in PWS (Chart 1).

Table 1 - Approximate guide to the development milestones in SPW

Smile	3-6 months
Sitting without support	13 months
Speaking single words	21 months
Floor	28 months
Speaking Phrases	3 years and 6 months

Source: Brazilian Prader Willi Syndrome Society (2022).

Other clinical features besides developmental delay include: cognitive impairment and behavior problems, obsessive-compulsive behavior, and skin lesions caused by self-aggression (the act of poking the skin). Some carriers of the syndrome may have psychological problems such as depression, violence, easy irritability and mood instability (EMERICK; VOGT, 2013).

Patients with PWS have both pituitary and hypothalamic dysfunction. When the pituitary gland begins to fail, there is usually a specific sequential failure of the pituitary hormones, starting with growth hormone (GH) and if not treated early, the cascading effect to dysfunction of the other pituitary hormones (LH, FSH, TSH, etc) begins. Hypothalamic dysfunction is characteristic of individuals with PWS, so clinical manifestations of pituitary hormone deficiency are expected (CATALETTO et al., 2011).

PWS patients develop hypothalamic dysfunction, which leads to various endocrinopathies such as: growth hormone deficiency, hypogonadism, hypothyroidism, central adrenal insufficiency, and low bone mineral density (HEKSCH et al., 2017). Hypothalamic dysfunction can also explain hyperphagia, temperature instability, high pain threshold, and sleep-disordered breathing (EMERICK; VOGT, 2013). The hypothalamus, in particular, is a major regulator of energy balance (ANGULO; BUTLER; CATALETTO, 2015)

For Passone et al. (2018), the main endocrine disorders found, in addition to those already mentioned above are: central adrenal insufficiency, hypothyroidism, hypogonadism, metabolic

syndrome, obesity, diabetes mellitus. It is common for patients to have other conditions such as sleep disorders, scoliosis, gastrointestinal problems, and coagulation disorders.

The most serious complication of the syndrome is obesity caused by binge eating and low caloric expenditure. Obesity leads to insulin resistance, cardiovascular and respiratory diseases that reduce the life expectancy of these patients, so the importance of emphasizing early treatment to prevent the complications generated by the syndrome (KUO et al., 2007).

4.2 DIAGNOSIS

Prader-Willi syndrome (PWS) is a complex genetic condition that arises due to the lack of expression of genes classified as imprinted on chromosome 15 and are paternally inherited. In the case of PWS, most genes in the region of chromosome 15q11-q13 are subject to genomic imprinting and only the alleles on the father-derived chromosome are active. These same maternal-derived chromosome 15 alleles are silenced by epigenetic factors and are normally not expressed. The absence of expression of one or more genes inherited from the father in the region of chromosome 15q11-q13 gives rise to the PWS phenotype and syndrome (BUTLER; MILLER; FORSTER, 2019).

This lack of expression can occur by three different genetic mechanisms that can lead to PWS. The first is paternal deletion in the chromosomal region 15q-11-q13, which accounts for 70% of cases. The other two subtypes are maternal uniparental disomy of chromosome 15, which accounts for 25% of cases, and the least common, which affects about 2% of syndrome carriers is abnormal methylation and gene expression pattern (PASSONE et al., 2018).

The clinical course of the syndrome differs from patient to patient and throughout their lives. Therefore, early diagnosis combined with multidisciplinary care can favorably alter the natural history of PWS. Therefore, the diagnosis of PWS should be confirmed very early during the neonatal period, thanks to the development of genetic testing (CRINÒ, et al., 2018).

A prenatal diagnosis is rarely made, but can theoretically be suspected in cases of reduced fetal movement and polyhydramnios. Genetic testing can be performed on samples obtained from chorionic villus sampling and amniocentesis. However, the few clinical laboratories that perform these tests in prenatal period (GOLDSTONE et al., 2008). Postnatal diagnosis is already possible in the first months of life because these infants present with severe hypotonia and other nonspecific symptoms (Table 1), where the physician suspects a genetic syndrome and refers for genetic testing (BAR et al., 2017).

The diagnosis of PWS is based on specific clinical features and is confirmed by genetic testing. Although diagnostic molecular testing for PWS is currently available, clinical identification of patients remains a challenge because many features of PWS are nonspecific, while others evolve over time or may be subtle (ELENA et al., 2012). Holm et al. (1993) proposed consensus clinical diagnostic criteria for PWS. However, Gunay-Aygun et al. (2001) proposed a revision of these diagnostic criteria (Table 1) to help identify appropriate patients for DNA testing. The suggested age ranges are based on characteristic stages in the natural history of PWS. Some features, such as neonatal hypotonia and feeding problems in infancy, help diagnose the syndrome during the early years of life, while others, such as overfeeding, are useful during early childhood.

Table 2 - Revised indications for DNA genetic testing

Age at Appraisal	**Characteristics to request DNA genetic test**
Birth to 2 years	Hypotonia with poor suction
2-6 years old	Hypotonia with a history of poor suction Global developmental delay
6-12 years old	History of hypotonia with poor suction (hypotonia usually persists Global developmental delay Overeating (hyperphagia, food obsession) with central obesity, if not controlled
13 years to adulthood	Cognitive impairment, usually mild mental retardation Overeating (hyperphagia, food obsession) with central obesity if not controlled Hypothalamic hypogonadism and/or typical behavior problems (including tantrums and obsessive-compulsive features)

SOURCE: Gunay-Aygun et al. (2001).

There are different genetic tests to confirm the diagnosis and identify the genetic subtype. Because imprinting genes demonstrate differential DNA methylation dependent on parental origin, patients with PWS have an exclusively maternal imprint because they do not have a paternal contribution. DNA methylation analysis is the only technique that can confirm and reject the diagnosis of PWS and therefore should be the initial investigation of choice. Parental samples are not required for this analysis. If the DNA methylation analysis shows only a maternal pattern, then PWS is confirmed (GOLDSTONE et al., 2008).

DNA methylation analysis in the Prader-Willi critical region detects the condition more than 99% of the time, and is then considered the first-line genetic test. However, further testing is needed to detect the genetic subtype. The deletion of the 15q11.2-q13 region of paternal

inheritance accounts for 70% of cases and can be determined by fluorescence in situ hybridization (FISH). Maternal uniparental disomy of chromosome 15 accounts for 25% of cases and can be determined by DNA polymorphism analysis in the syndrome carrier and in both parents. Imprinting defects account for most of the remaining 5% (EMERICK; VOGT, 2013).

For the study patient, what led the maternity doctors to order the genetic test was the presence of hypotonia and poor suction. Other differential diagnoses being ruled out, the main diagnostic hypothesis was a chromosomopathy. The test chosen by the geneticist for diagnosis was DNA methylation analysis, confirming the suspicion of Prader Willi Syndrome. As seen in the study, this exam is the ideal technique to confirm PWS.

As described, there are a range of clinical manifestations that can affect the quality and life expectancy of patients, but early diagnosis and management with a multidisciplinary team can prevent future complications and improve quality of life with lifelong care for patients (PASSONE et al., 2018).

In the absence of early diagnosis and treatment, the patient develops excessive weight gain, leading to severe early obesity between 3 and 4 years of age. Clinical suspicion is possible in the first months of life, as these babies have severe hypotonia, signaling the need for a genetic study (BAR et al., 2017). Therefore, the diagnosis of PWS can already be confirmed in the neonatal period, thanks to the development of genetic testing. All three major genetic subtypes (paternal exclusion, maternal uniparental disomy, and print center defects) can be detected in genetic tests (CRINÒ, et al., 2018).

The differential diagnosis of PWS consists of neuromuscular diseases and congenital myopathies, because of the similar signs and symptoms between the two (hypotonia). To study these diseases it is recommended to perform electroneuromyography and muscle biopsy. In the case of PWS, the biopsy is an invasive test, unnecessary, and shows nonspecific findings. Genetic testing, such as DNA methylation testing, avoids invasive procedures and ensures correct diagnosis (FRIDMAN et al., 2000).

Early diagnosis and appropriate multidisciplinary care are crucial for the baby's outcome, as they ensure parental guidance and support, including comprehensive counseling to prevent obesity and stimulation of cognitive and adaptive skills. In addition, the window of opportunity to achieve significant change is likely to be quite narrow, especially in relation to early brain plasticity, and late diagnosis may mean a missed opportunity for better quality of life in infants with PWS (BAR et al., 2017).

After diagnosis, it is critical to incorporate an interprofessional team such as a geneticist, endocrinologist, developmental specialist, nutritionist who can provide an integrated approach, and who will monitor disease progression and possible complications. They will assess the need for early initiation of complementary therapies to achieve better outcomes. This interprofessional team approach is necessary to optimize outcomes, patient quality of life, and longevity in patients with PWS (FERMIN GUITIERREZ; MENDEZ, 2022).

In Brazil, there is the Brazilian Prader Willi Syndrome Society (SPW BRASIL, 2022), affiliated to IPWSO (International Prader-Willi Syndrome). This organization helps parents, family members, and doctors understand more about the syndrome and how to live with it. The association was founded in 2016, in Rio de Janeiro, by parents of syndrome carriers. Today, in 2022, it has 300 families registered in the system, but they believe there are many more cases in Brazil, since it is a very underreported disease or late diagnosis. However, there is no study proving the incidence and/or the number of cases of PWS in Brazil (SPW BRASIL, 2022).

The goal of SPW BRASIL is to guarantee the right to a better quality of life for individuals with PWS. For this, they created a site where anyone can have access to medical alerts, basic guides about the syndrome for parents, doctors and health professionals. SPW BRASIL, is an essential tool to help, inform, and spread the importance of correct diagnosis and treatment. The association also has the help of a PWS treatment center at the State Institute of Diabetes and Endocrinology (IEDE) in Rio de Janeiro, and in São Paulo at the Hospital das Clínicas with multidisciplinary follow-up (SPW BRASIL, 2022).

4.3 CLINICAL MANAGEMENT

PWS is associated with a number of endocrinopathies, developmental and behavioral problems that should be evaluated and treated. Whenever possible, children with PWS should be referred to a multidisciplinary center familiar with the disease and the issues that must be addressed in the syndrome (MILLER, 2012).

According to Passone et al. (2018), the proposed treatment for these patients is follow-up protocol with the four main pillars: diet, exercise, GH replacement therapy, and behavioral and cognitive issues. In addition to a health maintenance schedule for children with PWS.

Proper nutrition is essential for the treatment of these patients. In the early years, poor suckling can lead to malnutrition, so many babies may need to be gavage-fed. In infancy, the child develops chronic hyperphagia, and incorrect feeding is a serious disorder that can lead to obesity

and life-threatening illnesses. Therefore, the diet should be controlled, with decreased caloric intake and monitoring with a nutritionist (ELENA et al., 2012).

Other non-pharmacological measures are also extremely important in the treatment of PWS. Physical activity helps in caloric expenditure, promotes socialization and helps to reduce binge eating. Physical therapy plays an essential role in improving hypotonia and respiratory capacity (ELENA et al, 2012). Psychological follow-up aimed at behavioral and cognitive strategies to help patients understand the expectation and rules and minimize compulsivity and aggression (FERMIN GUITIERREZ; MENDEZ, 2022).

Growth hormone deficiency (DGH), is the main endocrinopathy found in those with the syndrome. The prevalence of DGH ranges from 40 to 100% based on different studies (MUSCOGIURI et al., 2019). Due to the high prevalence of GH (growth hormone) deficiency, all patients with PWS should have GH replacement. The goal of GH therapy is to improve body composition (decrease fat mass, increase muscle mass) and promote growth. IQ also improves with GH therapy, especially in children with severe cognitive delays (ERHARDT; MOLNÁR, 2022).

The start of GH treatment should be as early as possible or soon after diagnosis. According to SPW Brazil, the benefits of starting treatment between 4 and 6 months have shown improvement in developmental markers of height, cognition, language, IQ, motor performance, and mobility. Some experts already recommend starting treatment at 3 months of age, with a dose equal to 1 mg/m²/day. It is noteworthy that hormone treatment should be indicated and monitored by an endocrinologist (SPW BRASIL, 2022).

Hypogonadism is present in both sexes and manifests as genital hypoplasia, incomplete pubertal development, and infertility in the vast majority. In boys, the penis may be small and the scrotum is hypoplastic, poorly rugose, and poorly pigmented. Unilateral or bilateral cryptorchidism is present in 80-90%. Human chorionic gonadotrophic hormone (hCG) is used to help patients lower the position of the testes, although a significant percentage of them still require orchipexy (MILLER, 2012).

In both sexes, hypogonadism will lead to no puberty or late and incomplete puberty. Because of this, almost all individuals will require hormone treatment for induction, promotion or maintenance of puberty (GOLDSTONE et al., 2008).

Two other endocrinopathies that are very frequent in children with PWS are hypothyroidism and adrenal insufficiency. Therefore, blood levels of T4 and TSH should be collected at birth and checked annually for thyroid control. The administration of glucocorticoids

during episodes of moderate/severe stress is also recommended to prevent cases of adrenal insufficiency (ELENA et al., 2012).

As seen in the clinical case, the period that the patient stayed in the maternity ward, the team of doctors, worked for two months trying to find the cause of the hypotonia. During this period, treatment was directed at the adverse manifestations that the patient presented. A characteristic passage of the syndrome was that as she did not gain weight, gavage was necessary. The respiratory difficulty was circumvented with inhaled oxygen therapy. During this period of hospitalization, the treatment was supportive, until the source of the symptoms was discovered.

After the diagnosis, the patient is followed by a multidisciplinary team, including a pediatrician, endocrinologist, nurses, physical therapy for motor and respiratory development, nutritionist, and social worker. Everyone works towards improving the quality of life and trying to reach the developmental milestones for her.

Due to the range of clinical manifestations among patients, patient management must be adapted, but also to the variability in the same patient throughout his or her life. Therapeutic decisions and clinical follow-up need to consider each problem a patient may face (ELENA et al., 2012).

The prognosis of those with Prader Willi Syndrome will depend on the early clinical course and the degree of complications. Patients who have early diagnosis and continuous treatment throughout life can achieve an average life expectancy. Death usually occurs in the fourth decade of life if comorbidities are not well controlled, but if they are controlled, they may live longer (FERMIN GUITIERREZ; MENDEZ, 2022).

"Although PWS has no cure, technological advances in more sensitive genetic testing have helped improve quality of life through early diagnosis and intervention" (CATALETTO et al., 2011, p. 10). "Prader Willi Syndrome is an example of how early diagnosis and treatment can significantly improve long-term outcome despite genetic background" (ELENA et al., 2012, p. 1).

5 CONCLUSION

As a conclusion, it can be inferred that PWS is a rare genetic disease, known as the main cause of obesity in children. The diagnostic hypothesis should already be considered when a hypotonic newborn is found, and early diagnosis is fundamental, as it can prevent complications and improve the quality of care throughout the patient's life.

It is worth mentioning that no medication is available to treat or cure this genetic disorder. Therefore, carriers of PWS must be followed by a multidisciplinary team composed of

neonatologists, pediatricians, endocrinologists, geneticists, psychologists, therapists, nutritionists, and physical therapists. Through the articulation of knowledge of these specialists it is possible to prevent complications and prolong the life expectancy of this group.

This work is extremely important for the pediatric area, because it will ease/guide the family and the doctors about what the main clinical manifestations are, how the diagnosis is made, and the importance of early diagnosis, besides showing the main pillars available for treatment and follow-up of the syndrome.

However, since Prader Willi Syndrome was first described in the literature less than 70 years ago, more studies are still needed in this area in order to develop and elucidate new ways of managing the disease.

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