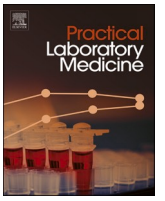
Practical Laboratory Medicine 40 (2024) e00405

Contents lists available at ScienceDirect

Practical Laboratory Medicine

journal homepage: www.elsevier.com/locate/plabm



A genetic condition that spans both extremes of the nutritional spectrum

Lisa M. Johnson [a, b, *]

[a] Department of Laboratories, Seattle Children's Hospital, Seattle, WA, 98105, USA
[b] Department of Laboratory Medicine and Pathology, University of Washington, WA, 98195, USA

ARTICLE INFO

Keywords:
Prader Willi syndrome
Nutrition
Obesity
Hyperphagia
Pediatric

ABSTRACT

Prader-Willi syndrome (PWS) is a complex genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region, known as the Prader Willi critical region. Nutritional clinical manifestations change with age and are described in four different phases. The phases span both extremes of the nutritional spectrum, beginning with an infant with poor sucking reflexes and failure to thrive then progressing to an adolescent who may have hyperphagia and be at risk for obesity. The phenotype is likely due to hypothalamic dysfunction due to genetic changes in the Prader Willi critical region. Researchers are examining the pathological mechanisms that determine the disease course.

1. Case description

An 11-year-old female was seen at a children's hospital for a routine follow-up appointment. Current medical concerns include obstructive sleep apnea, excess weight gain, mild scoliosis, growth hormone deficiency, and central hypothyroidism. She has gained approximately 5 kg in the past year, moving from the 61st percentile weight-for-age to the 78th percentile weight-for-age. Medications include growth hormone injections and levothyroxine. Laboratory orders consisted of a complete blood count (CBC), cortisol, ferritin, Insulin-like Growth Factor 1 (IFG-1), Insulin-like Growth Factor-binding Protein 3 (IGF BP-3), free thyroxine, fasting plasma glucose, electrolytes, hemoglobin A1c, and vitamin D. All results were unremarkable, except for a slightly low vitamin D of 28 nmol/L.

During discussion with the pediatric endocrinologist, the patient reported feeling hungry all the time and food intake was closely monitored. The parents secured excess food in the home because the patient has hyperphagia, a condition in which she cannot control her appetite and will eat in excess. The young patient is closely monitored by a multidisciplinary healthcare team, including an endocrinologist, dietician, sleep specialist, and orthopedic specialist, for Prader Willi Syndrome.

2. Discussion

Prader Willi Syndrome (PWS) is one of the most common causes of genetic obesity, with an incidence rate of approximately 1 in 10,000 to 1 in 25,000 live births. The condition was first described by Swiss researchers, Andrea Prader, Heinrich Willi, and Alexis Labhart, in 1956 as children with feeding difficulties, poor muscle tone, underdeveloped sex organs, short stature, small hands and feet, and some cognitive and behavioral impairments [1,2]. Genetic testing can diagnose the condition which is caused by the absence

* Department of Laboratories, Seattle Children's Hospital, Seattle, WA, 98105, USA
E-mail address: lisa.johnson2@seattlechildrens.org.

https://doi.org/10.1016/j.plabm.2024.e00405
Received 3 July 2023; Accepted 21 May 2024
Available online 23 May 2024

of expression of imprinted genes in the paternally derived region of chromosome 15q11-q13, also known as the Prader Willi critical region [3].

Loss of genetic expression from the Prader Willi critical region results in impaired hypothalamic development and function. The hypothalamus is important for homeostasis of the autonomic nervous system and endocrine hormones. Disruption of the hypothalamic-pituitary axis causes a range of hormone abnormalities for patients with PWS, such as growth hormone deficiency, hypogonadism, hypothyroidism, premature adrenarche, corticotropin deficiency, and precocious puberty [1]. Patients with PWS also have impaired levels of the hypothalamic hormone oxytocin, as well as altered signaling in hunger hormones. These hormones likely play a role in the hyperphagia, or extreme insatiable hunger, that is characteristic of older children with PWS [1,4].

Nutritional deficiencies in PWS were described in a seminal paper by Miller et al. in four different phases [5]. Interestingly, patients with PWS go through extreme opposites of the nutritional spectrum, starting out as an anorexic newborn with failure to thrive and progressing to a young adult at risk for obesity and hyperphagia. Miller et al. defined Phase 0 as intrauterine growth restriction and reduced fetal movements, which can sometimes lead providers to suspect an issue with the developing fetus. Phase 1 describes the state of the infant after birth as hypotonic with poor sucking reflexes that cause feeding difficulties. Many will need assistance from a nasogastric tube to receive adequate nutrition. During development, patients with PWS have an altered body composition, with increased body fat, lower muscle mass, and short stature. Currently, the only FDA approved medication for PWS is to begin growth hormone treatment a couple months after birth to increase growth and muscle mass [1]. With treatment, most infants with PWS will achieve normal weight gain with appropriate growth compared to peers by the end of Phase 1.

The shift in nutritional deficiencies begins during the toddler stage. Phase 2 is marked by excessive weight gain, with a substantial change in appetite and caloric intake. Since patients with PWS have an altered body composition, it is important that they receive nutritional guidance to control weight through diet and exercise. A 20–40 % reduced calorie diet that is nutrient-rich and well-balanced in fats, carbohydrates, and protein will help the patient maintain a healthy weight [4,6]. During Phase 3, a patient with PWS experiences marked hyperphagia, with strong food-seeking behaviors and an insatiable appetite. This is often stressful for caregivers, since food must be carefully stored in locked or inaccessible areas. Not only is the patient at high risk for developing obesity, but there is also a higher incidence of choking while consuming too much food [7]. And finally, in Phase 4, some patients with PWS will experience satiety during adulthood [1,5].

Several groups are researching the mechanism of hyperphagia in patients with PWS [4,6]. This behavior contributes to the risk for developing morbid obesity with the associated co-morbidities of sleep apnea, type 2 diabetes, hypertension, and cardiovascular disease. Obesity in patients with PWS ranges from around 40 % in childhood and 82–98 % in adults, and it appears to be caused by several regions of dysregulation [4]. First, patients have an imbalance in hunger hormones, with increased concentrations of ghrelin and insulin and decreased concentrations of leptin, adiponectin, pancreatic polypeptide, and peptide YY. Second, there is impaired hypothalamic pathways of satiety control which may involve oxytocin secretion and receptors for ghrelin and insulin. Lastly, patients with PWS have an altered body composition with reduced energy expenditure than their aged-matched peers. All of these complexities likely play a role in the development of obesity in patients with PWS [4]. Current research has explored the use of oxytocin analogues, hunger hormone modifiers (GLP-1 receptor agonists, inhibitors of ghrelin processing, metformin and other diabetic medications), and bariatric surgery to prevent obesity, but more research is needed to understand what drives the mechanism of hyperphagia [4,8].

A collaborative healthcare effort from a multi-disciplinary team is needed to care for these patients. Laboratory results play an important role in monitoring the endocrine and nutritional deficiencies [5]. Vitamin D is monitored closely because lower bone density is associated with increased risk of scoliosis and osteoporosis in patients with PWS. Additionally, a lipid panel, insulin, fasting glucose, and hemoglobin A1c are screened during childhood. Table 1 shows a panel of laboratory tests that helps providers follow these patients during development [8].

Given that the disease is rare, research is trying to expand animal and cellular models to test various therapeutic options. Although a handful of clinical trials have been attempted, researchers have not found an ideal therapeutic option to control the symptoms of hyperphagia and development of obesity in PWS [5,8]. Some researchers believe that different medications may work best during different phases of development. For example, oxytocin analogues helped newborns develop an appetite for healthier weight gain, while GLP-1 analogues had some success with weight loss for young adults with obesity. Alternative, other researchers think that the specific therapeutic option may need to be paired with the specific genetic abnormalities seen for PWS [6]. The Prader Willi critical region contains five uniquely expressed genes (MKRN3, MAGEL2, NECDIN, SNURF-SNRPN) and a family of six small nucleolar RNA genes [3]. Animal models of PWS with single gene deletions will help researchers understand the role and pathological mechanism of

Table 1
Recommended laboratory tests for patients with Prader Willi syndrome.

Age Range	Laboratory Tests
Infant	IGF1, IGFBP3, thyroid studies, 25-OH vitamin D
1 month- 1 year	IGF1, IGFBP3, thyroid studies, 25-OH vitamin D, *CBC, vitamin B12, adrenal studies, iron studies*[a]
1–5 years	IGF1, IGFBP3, thyroid studies, 25-OH vitamin D, CBC, vitamin B12, adrenal studies, iron studies, c*alcium, electrolytes, lipid panel*[a]
5–13 years	IGF1, IGFBP3, thyroid studies, 25-OH vitamin D, CBC, vitamin B12, adrenal studies, iron studies, calcium, electrolytes, lipid panel, *hemoglobin A1c, insulin, fasting glucose, puberty evaluation (if clinically indicated)*[a]
13–21 years	IGF1, IGFBP3, thyroid studies, 25-OH vitamin D, CBC, vitamin B12, adrenal studies, iron studies, calcium, electrolytes, lipid panel, hemoglobin A1c, insulin, fasting glucose, puberty evaluation (if clinically indicated), *oral glucose tolerance test*[a]

[a] Italicized tests are new tests added during that stage of development.

these genetic changes, which will aid in therapeutic development [9]. This research is benefitting other disorders of hypothalamic obesity, since treatment may need to be personalized based on the specific genes impacted and the stage of development [3,9].

Although nutritional concerns are highly prevalent in patients with PWS, careful monitoring by a multi-disciplinary team has improved the quality and length of life for these patients. The patient described in the case presentation is doing quite well and in a healthy state, given the disease course and limited treatment options. Research is promising to help elucidate the role of the different genes that contribute to the symptoms of obesity and hyperphagia in PWS, which will hopefully lead to better therapeutic options for these patients.

This case report was submitted to the Seattle Children's Institutional Review Board and deemed exempt as research.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

LMJ received support for travel and attendance at the AACC Annual Scientific Meeting. No funding was required for this case report.

Data availability

This case report was submitted to the Seattle Children's IRB and deemed exempt as research.

References

[1] M. Tauber, C. Hoybye, Endocrine disorders in Prader-Willi syndrome: a model to understand and treat hypothalamic dysfunction, Lancet Diabetes Endocrinol. 9 (4) (2021 Apr) 235–246.
[2] Y. Hu, X. Xue, J. Fu, Case report: clinical analysis of seven neonates with Prader-Willi syndrome and review of the literature, Front Pediatr 9 (2021 Feb 18) 633532. PMID: 33681108.
[3] S.B. Cassidy, S. Schwartz, J.L. Miller, et al., Prader-Willi syndrome, Genet. Med. 14 (1) (2012 2012/01/01) 10–26.
[4] M.J. Khan, K. Gerasimidis, C.A. Edwards, et al., Mechanisms of obesity in Prader–Willi syndrome, Pediatr. Obes. 13 (1) (2018) 3–13.
[5] J.L. Miller, C.H. Lynn, D.C. Driscoll, et al., Nutritional phases in Prader-Willi syndrome, Am. J. Med. Genet. 155a (5) (2011 May) 1040–1049.
[6] Q. Tan, C.E. Orsso, E.C. Deehan, et al., Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: a narrative review, Obes. Rev. 21 (5) (2020 May) e12992.
[7] D.A. Stevenson, J. Heinemann, M. Angulo, M.G. Butler, J. Loker, N. Rupe, P. Kendell, C.L. Clericuzio, A.O. Scheimann, Deaths due to choking in Prader-Willi syndrome, Am. J. Med. Genet. 143A (5) (2007 Mar 1) 484–487, https://doi.org/10.1002/ajmg.a.31502. PMID: 17036318; PMCID: PMC3243066.
[8] J. Duis, P.J. van Wattum, A. Scheimann, et al., A multidisciplinary approach to the clinical management of Prader–Willi syndrome, Mol. Genet. Genom. Med. 7 (3) (2019) e514.
[9] K.V. Carias, R. Wevrick, Preclinical testing in translational animal models of Prader-Willi syndrome: overview and gap analysis, Mol. Ther. Methods Clin. Dev. 13 (2019 Jun 14) 344–358.