STM JOURNALS

Research & Reviews: A Journal of
Pharmacology

ISSN: 2230-9861 (Online)
ISSN: 2349-1299 (Print)
Volume 14, Issue 2, 2024
May–August
DOI (Journal): 10.37591/RRJoP

https://journals.stmjournals.com/rrjop

Review RRJoP

Current Perspectives of Prader-Willi Syndrome: A Multisystem Approach

Sreelekshmy B.S.[1], Ranjana S.R.[1], Shaiju S. Dharan[2], Amal A.[3,*]

Abstract

Prader-Willi syndrome (PWS) is a genetic disorder with multisystem involvement, caused by the lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region from paternal 15q11-q13 deletions (about 60%), or maternal uniparental disomy 15, or both. It is a complex and contiguous gene disorder which affects the multiple systems with many clinical presentations, especially hypothalamic insufficiency. The clinical features are characterized by short stature position, developmental delay, and cognitive and behavioral disorders. The major causes of morbidity and mortality in PWS individuals are obesity and behavioral problems. Specific diagnostic criteria for PWS are both the methylation analysis and the oligo-SNP combination array (OSA). Early diagnosis is needed for the effective management. There is no cure with a single intervention. Management is symptomatic, which includes hormone replacement therapies, behavioral management, control of food intake and patient education. Currently, there is no approved therapy for the management of hyperphagia in PWS. Usually, PWS is identified in infancy by genetic test. Genomic changes, such as loss of expression of genes on chromosomes 15q11.2-q13, occur due to failures in gene expression. DNA methylation analysis is a powerful tool to access paternal-only, maternal-only or biparental inheritance. This analysis helps to identify the deletion in the majority of individuals with PWS. Another diagnostic option for PWS is Microsatellite analysis. Nutritional counselling for long term weight management is necessary to prevent the inappropriate weight gain, which begins at the age between 1 and 3 years. Growth hormone replacement therapy improves growth and ultimate height, muscle function and level of activity. Psychological and psychosocial considerations are essential for PWS.

Keywords: Prader-Willi syndrome, hypogonadism, obesity, genetic mutation, hyperphagia

***Author for Correspondence**
Amal A.
E-mail: amalapps4@gmail.com

[1]Pharm D Intern, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkara, Thiruvananthapuram, Kerala, India
[2]Principal/HOD, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkara, Thiruvananthapuram, Kerala, India
[3]Assistant Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkara, Thiruvananthapuram, Kerala, India

Received Date: July 16, 2024
Accepted Date: August 09, 2024
Published Date: August 12, 2024

Citation: Sreelekshmy B.S., Ranjana S.R., Shaiju S. Dharan, Amal A. Current Perspectives of Prader-Willi Syndrome: A Multisystem Approach. Research & Reviews: A Journal of Pharmacology. 2024; 14(2): 42–48p.

INTRODUCTION

The syndrome was first described by Langdon Down in 1887, London. And later, the Prader-Willi syndrome was named by Prader, Labhart and Willi in 1956. Prader-Willi syndrome (PWS) is a multisystem genetic disorder caused by the failure of expression of genes on the paternally inherited chromosome 15q11.2-q13 region from paternal 15q11-q13 deletions (about 60%), or maternal uniparental disomy 15, or both [1, 2]. An estimated prevalence in several studied populations in 1/10,000–1/30,000. PWS was the first shown to be caused by uniparental disomy. It results from lack of expression of paternally inherited genes in the PWS region of chromosome 15 [2], which is, both chromosome 15s are inherited from the mother. The cardinal clinical manifestations include severe infantile hypotonia, hyperphagia with obesity during early childhood, developmental delay with

learning and behavioral problems, small hands or feet and hypogonadism or hypogenitalism and other endocrine deficiencies [3]. Individuals with PWS typically have intellectual disability and show behavioral disturbances when it is compared with unknown etiology [4]. Due to the combination of severe infantile hypotonia and intellectual disabilities, individuals may experience speech and language difficulties [5]. Sometimes individuals are presented with psychosis. The PWS child may develop hyperphagia during the initial stage of infancy that leads to advanced obesity and this is mostly caused by hypothalamic dysfunction [6]. These dysfunctions are responsible for growth hormone deficiency and thyroid stimulating hormone deficiency, central adrenal insufficiencies and hypogonadism. The most common cause of death is respiratory failure and is followed by cardiac failure and gastro intestinal failure infections [7, 8].

Early diagnosis is needed for the effective management. There is no cure with a single intervention [6]. Management is symptomatic, including hormone replacement therapies, behavioral management, controlling food intake and patient education [9]. Currently, there is no approved therapeutics for the treatment of hyperphagia in PWS. Nowadays, PWS is the most common known cause of syndromic obesity and also common cause of obesity related mortality [7]. This review highlights on current evidence regarding Prader-Willi syndrome and its management.

ANNALS OF PRADER-WILLI SYNDROME

The natural cause of PWS has several nutritional phases with complex progression including phase 0 to phase 4 (phase 0, phase 1A, phase1B, phase 2A, phase 2B, phase 3, phase 4) [10]. Phase 0/prenatal phase characterized with decreased fetal activity, polyhydramnios, intra uterine growth restriction breech presentation, lower birth weight than siblings and small for gestational age [11]. Phase 1/hypotonia (at birth), during phase 1A (0–9 months), poor feeding and sucking develops. This requires use of feeding through other methods. In Phase 1B (9–24 months), infants begin to feed more accurately along a disease specific growth chart [12, 13]. Phase 2 involves, transition from anorexia to obesity. In phase 2A (2–4.5 years), weight gain occurs with a growth curve without an increased calorie intake. In Phase 2B (4.5–8 years), increased appetite compared to earlier with continued weight gain along with interest in food [14]. During Phase 3 (8 years-adult), hyperphagia with uncontrolled appetite. They exhibit food seeking behaviors to obtain food. Phase 4/adults includes some of the PWS patients. They show improvement in appetite control and ability to feel gorged after eating [9]. The correct mechanism of nutritional phases is unknown.

Clinical Manifestations

Hypotonia and neurological dysfunction: Hypotonia is prenatal; in onset, there is decreased in movement and lethargy in infancy with poor weight gain and poor sucking ability that leads to early feeding difficulties. Mild to moderate hypotonia persist throughout life [9].

Hypogonadism: Hypogonadism leads to genital hypoplasia throughout the lifetime. Incomplete pubertal development and infertility also occurs in PWS individuals. This results in decreased or absent growth and reduced height [15–17]. Cryptorchidiso is present in 80–90% of cases.

Hyperphagia and obesity: The frequency of obesity in PWS varies from 40% in children and 82–98% in adults [15, 16]. Body composition is abnormal in PWS patients with normal body fat. Obesity is the major cause of morbidity and mortality in this cases, that is, 25% of obese individuals have type 2 diabetes mellitus [18].

Developmental and congenital delays: Congenital disability plays evidence by school age. In most conditions, PWS individuals are mentally retarded, have delayed psychomotor development, and impaired skeletal growth. These individuals show severe learning disability and poor academic performance.

Psychiatric and behavioral disturbances: Psychiatric and behavioral problems become more prominent in adolescents and adulthood. 70–90% affected individuals have behavioral and psychiatric

disturbances. These include manipulating behavior stubbornness, temper tantrums and deficit of emotional regulation [19]. The severity of behavioral disturbances increases with age and body mass index (BMI) [20].

Sleep abnormalities: PWS individuals experience central and obstructive sleep apnea, abnormal circadian rhythm in REM sleep, abnormal arousal and abnormal response to hypercapnia [21, 22]. Obesity is also a factor, which can worsen the sleep disorder.

Genetics in Prader Willi Syndrome

Usually, PWS is identified in infancy by genetic test. The genomic changes cause loss of expression of the genes on chromosomes 15q11.2-q13 through loss of failure of expression [23]. Most cases result from deletion of 5-7 Mb in 15q11.2-q13. About 60–70% cases of PWS are caused by deletion of paternally inherited PWS locus (Type I and Type II) and 25–30% by maternal uniparental disomy. PWS is usually caused by spontaneous mutation [24]. The region of genome involved in PWS is shown in Figure 1. The genetic phenomena are not completely understood, but in PWS, there is differential silencing of genes in a parent-of-origin-dependent pattern. Thus, PWS is caused by the loss of paternal expression of the gene in PWS critical region (15q11.2-q13) [25]. Other genetic mechanism included in PWS are maternal uniparental disomy (UPD 15) and imprinting defects (ID).

Diagnosis

The diagnosis of PWS is complicated in its origin. Initially it is identified by its clinical presentation and the genetic confirmation was first discovered by Ledbetter *et al.* [26]. DNA methylation analysis (methylation-specific-multiplex ligation-dependent probe amplification analysis/MS-MLPA) is a powerful tool to access paternal-only, maternal-only or biparental inheritance [27].

In PWS, individuals have only the maternal methylated allele, whereas in normal individuals, there is a presence of both methylated and unmethylated allele. Therefore, the most specific analysis to diagnose PWS is DNA methylation analysis, which helps to identify the deletion and this is seen in most of individuals with PWS. Another diagnostic option was Microsatellite analysis which is necessary as only MS-MLPA does not show deletion in critical PWS region. It shows UDP and hetrodisomy or isodisomy (Figure 2) [6].

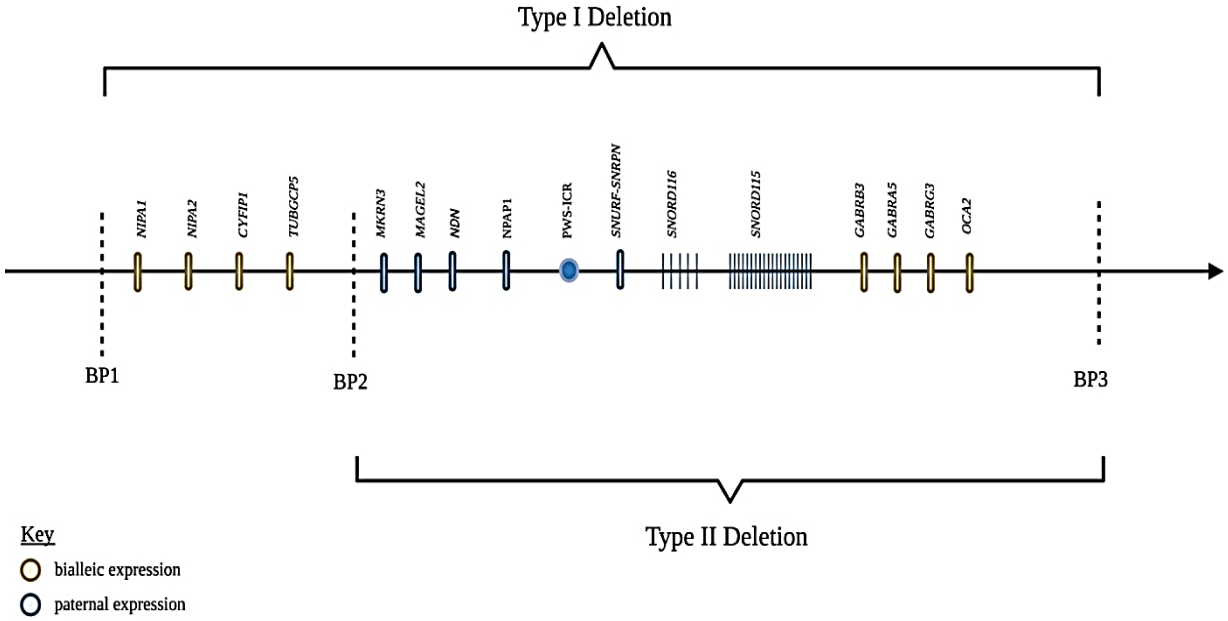

Figure 1. Genes in the PWS critical region, chromosomes 15q11.2-q13. Created with BioRender.com (accessed on 25 March 2022).

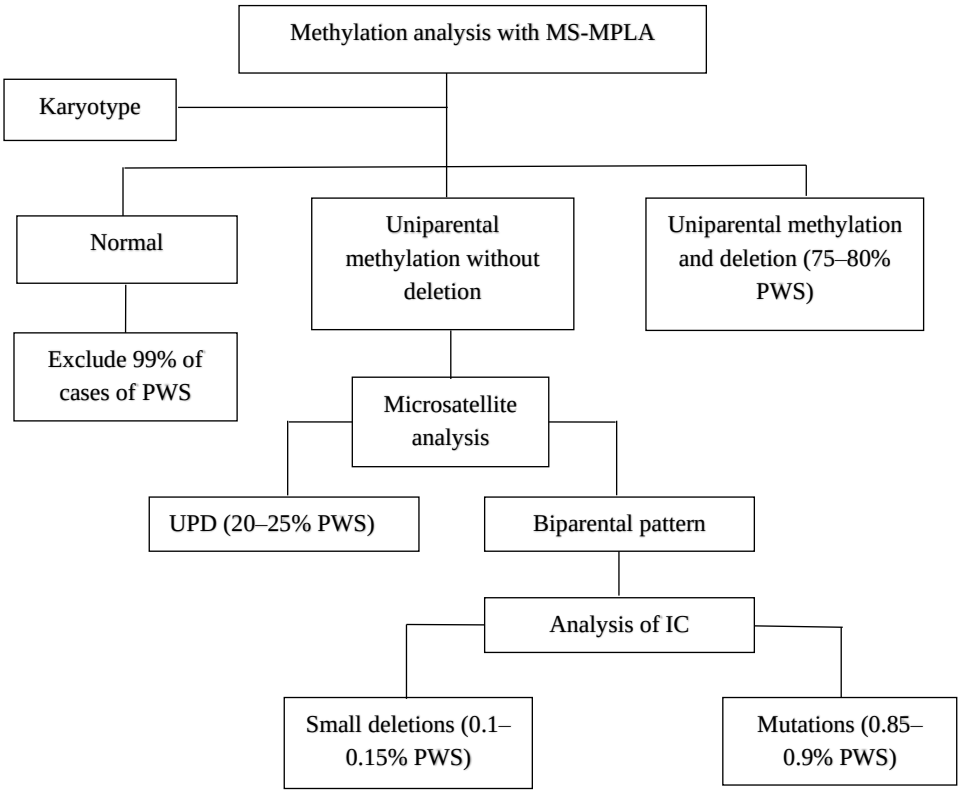

Figure 2. Algorithm for genetic testing for PWS. MS-MPLA: methylation-specific-multiplex ligation-dependent probe amplification analysis. *UPD:* Uniparental Disomy. *IC:* Impainting Centre.

Management

Management of PWS is very age dependent and which is focused on anticipatory guidance. Nutritional counselling for long term weight management is necessary to prevent the inappropriate weight gain, which starts at the age between 12 and 36 months (1–3 years). One of the vital parts is to monitor growth and record measurement on a standard growth curve. There is no known pharmacological agent present for hyperphagia. The diet should have a balance to distribution and which should be rich in fiber with a calorie intake about 70–80% [6]. Recent studies regarding psychiatric side effects need careful monitoring in PWS individuals.

Pharmacological Approach

Growth hormone (GH) therapy in infants, children and adults are demonstrated in well-designed and well-controlled studies [28–30]. The dosage of growth hormone begins at 0.5 up to 1 mg/m^2. Growth hormone replacement therapy improves linear growth and height, muscle function and level of activity. GH helps in maintaining muscle mass and body composition in adults. Premature adrenarc has been reported to occur more commonly [29]. It is not recommended in uncontrolled diabetes, malignancy and critical illness. There is a controversy among experts about role of GH in unexpected death [31, 32]. Risk of growth hormone includes sleep apnea and increased blood sugar. First line therapies of obesity and hyperphagia in PWS are nutritional support and behavioral therapies. Topiramate is recently used as experimental appetite suppressant for PWS when compared with behavioral and educational therapy. Topiramate has made significant effect on preventing hyperphagia. There are also other drugs currently being investigated for use in PWS.

Cryptorchidism is common in males and this requires surgical intervention. Pubertal deficiency is treated with hormone replacement therapy (sex hormone) which helps in adequate production of secondary sexual characteristics. But possibly sex hormone replacement causes behavioral problems in males and increased risk of stroke in females [33]. Sex education is needed in case of risk of sexually

transmitted diseases and rare pregnancy. Social skills' training is needed; this helps to focus on learning and diminish behavioral problems. The psychiatric problems should be treated according to parental education or training otherwise, pharmacological approaches can be taken. For example, serotonin agonist is successful in reducing temper and compulsivity [34, 35].

From the current literature, hypogonadism frequently occurs in males and females and is caused due to spontaneous puberty. Psychological and psychosocial considerations are important for PWS. PWS individuals are at risk for central adrenal insufficiency. And also, LH or FSH disturbances are also reported after GI problems which are then followed by PSH and ACTH with pituitary hormone deficiency [36]. Currently, gene therapy is being explored as a treatment for PWS by replacing mutated genes with new gene or modified gene through direct alteration to the patient's genetic material.

CONCLUSION

Prader-Willi syndrome (PWS) is a genetic, complex and multisystem disorder. Clinically, the most vital need is to identify the cause of PWS. It also helps mental health, hypotonia, hypophagia and high risk of obesity. Individuals with PWS will have various problems, so they should undergo patient specific treatment. Early diagnosis is the key that helps in initiation of GH treatment, controlled diet, regular physical activity and mental health and development. Nowadays, PWS has improved and the treatment options are getting vast. There are several studies, which are ongoing related to physical and mental issues. Prevention of complications and prolong life expectancy can improve quality of life of PWS individuals.

REFERENCES

1. Muscogiuri G, Barrea L, Faggiano F, Maiorino MI, Parrillo M, Pugliese G, Ruggeri RM, Scarano E, Savastano S, Colao A, RESTARE. Obesity in Prader–Willi syndrome: Physiopathological mechanisms, nutritional and pharmacological approaches. J Endocrinol Invest. 2021; 44(10): 2057–70.
2. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012; 14(1): 10–26.
3. Butler MG, Miller JL, Forster JL. Prader-Willi syndrome-clinical genetics, diagnosis and treatment approaches: an update. Curr Pediatr Rev. 2019; 15(4): 207–44.
4. Curfs LM, Verhulst FC, Fryns JP. Behavioral and emotional problems in youngsters with Prader-Willi syndrome. Genetic Counseling (Geneva, Switzerland). 1991; 2(1): 33–41.
5. Lewis BA, Freebairn L, Heeger S, Cassidy SB. Speech and language skills of individuals with Prader-Willi syndrome. Am J Speech-Lang Pathol. 2002; 11(3): 258–294.
6. Elena G, Bruna C, Benedetta M, Stefania DC, Giuseppe C. Prader-Willi syndrome: clinical aspects. J Obes. 2012; 2012(1): 473941. https://doi.org/10.1155/2012/473941
7. Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. Genet Med. 2017; 19(6): 635–42.
8. Manzardo AM, Loker J, Heinemann J, Loker C, Butler MG. Survival trends from the Prader–Willi syndrome association (USA) 40-year mortality survey. Genet Med. 2018; 20(1): 24–30.
9. Cassidy SB, Driscoll DJ. Prader–willi syndrome. *Eur J Hum Genet*. 2009; 17(1): 3–13. https://doi.org/10.1038/ejhg.2008.165
10. Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, Dykens E, Butler MG, Shuster JJ, Driscoll DJ. Nutritional phases in Prader–Willi syndrome. Am J Med Genet A. 2011; 155(5): 1040–9. https://doi.org/10.1002/ajmg.a.33951
11. Butler MG, Lee PD, Whitman BY, editors. Management of Prader-Willi Syndrome. New York: Springer Nature; 2006.
12. Gross N, Rabinowitz R, Gross-Tsur V, Hirsch HJ, Eldar-Geva T. Prader–Willi syndrome can be diagnosed prenatally. Am J Med Genet A. 2015; 167(1): 80–5.

13. Lee J, Isojima T, Chang MS, Kwun YH, Huh R, Cho SY, Sohn YB, Jin DK. Disease-specific growth charts for Korean infants with Prader–Willi syndrome. Am J Med Genet A. 2015; 167(1): 86–94.
14. Rosenbloom ST, Butler MG. Development and implementation of electronic growth charts for infants with Prader–Willi syndrome. Am J Med Genet A. 2012; 158(11): 2743–9.
15. Crino A, Schiaffini R, Ciampalini P, Spera S, Beccaria L, Benzi F, Bosio L, Corrias A, Gargantini L, Salvatoni A, Tonini G. Hypogonadism and pubertal development in Prader-Willi syndrome. Eur J Pediatr. 2003; 162(5): 327–33.
16. Tauber M, Hoybye C. Endocrine disorders in Prader-Willi syndrome: a model to understand and treat hypothalamic dysfunction. Lancet Diabetes Endocrinol. 2021; 9(4): 235–46.
17. Noordam C, Höybye C, Eiholzer U. Prader–willi syndrome and hypogonadism: A review article. Int J Mol Sci. 2021; 22(5): 2705.
18. Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T. Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. Dev Med Child Neurol. 2002; 44(4): 248–55.
19. Schwartz L, Caixàs A, Dimitropoulos A, Dykens E, Duis J, Einfeld S, Gallagher L, Holland A, Rice L, Roof E, Salehi P. Behavioral features in Prader-Willi syndrome (PWS): consensus paper from the International PWS Clinical Trial Consortium. J Neurodev Disord. 2021; 13: 25(3p).
20. Steinhausen HC, Eiholzer U, Hauffa BP, Malin Z. Behavioural and emotional disturbances in people with Prader–Willi syndrome. J Intellect Disabil Res. 2004; 48(1): 47–52.
21. Nixon GM, Brouillette RT. Sleep and breathing in Prader-Willi syndrome. Pediatr Pulmonol. 2002; 34(3): 209–17.
22. Yee BJ, Buchanan PR, Mahadev S, Banerjee D, Liu PY, Phillips C, Loughnan G, Steinbeck K, Grunstein RR. Assessment of sleep and breathing in adults with Prader-Willi syndrome: a case control series. J Clin Sleep Med. 2007; 3(7): 713–8.
23. Glenn CC, Driscoll DJ, Yang TP, Nicholls RD. Genomic imprinting: potential function and mechanisms revealed by the Prader-Willi and Angelman syndromes. Mol Hum Reprod. 1997; 3(4): 321–32.
24. Cassidy Suzanne B, Stuart Schwartz, Miller Jennifer L, Driscoll Daniel J. Prader-Willi syndrome. Genet Med. 2012; 14(1): 10–26. https://doi.org/10.1038/gim.0b013e31822bead0.
25. Tucci V, Isles AR, Kelsey G, Ferguson-Smith AC, Bartolomei MS, Benvenisty N, Bourc'his D, Charalambous M, Dulac C, Feil R, Glaser J. Genomic imprinting and physiological processes in mammals. Cell. 2019; 176(5): 952–65.
26. Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Keenan BS, Crawford JD. Deletions of Chromosome 15 as a Cause of the Prader-Willi Syndrome. N Engl J Med. 1981; 304(6): 325–329.
27. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010; 86(5): 749–64.
28. Lindgren AC. Somatropin therapy for children with Prader-Willi syndrome: guidelines for use. Treat Endocrinol. 2006; 5(4): 223–8.
29. Angulo MA, Castro-Magana M, Lamerson M, Arguello R, Accacha S, Khan A. Final adult height in children with Prader–Willi syndrome with and without human growth hormone treatment. Am J Med Genet Part A. 2007; 143(13): 1456–61.
30. Höybye C. Five-years growth hormone (GH) treatment in adults with Prader-Willi syndrome. Acta Paediatr. 2007; 96(3): 410–3.
31. Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, Kendell P, Cassidy SB, Scheimann A. Gastric rupture and necrosis in Prader–Willi syndrome. J Pediatr Gastroenterol Nutr. 2007; 45(2): 272–4.
32. Carrel AL, Lee PD, Mogul HR. Growth hormone and Prader-Willi syndrome. Management of Prader–Willi syndrome. New York: Springer; 2022: 195–216.

33. Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. J Clin Endocrinol Metab. 2006; 91(2): 413–7.
34. Brice JA. Behavioral and psychotropic interventions in persons with Prader-Willi syndrome. The Endocrinologist. 2000; 10(4): 27S–30S.
35. Dykens E, Shah B. Psychiatric disorders in Prader-Willi syndrome: epidemiology and management. CNS drugs. 2003; 17(3): 167–78.
36. Melmet S, Jameson JL. Disorders of the anteritary and hypothalamus. In: Jameson JL, editor. Harrison's Endocrinology. 3rd Edn. New York: McGraw-Hill; 2013; 16–49.

