Clinical Autonomic Research (2023) 33:281–286
https://doi.org/10.1007/s10286-022-00909-7

REVIEW ARTICLE

Autonomic nervous system dysfunction in Prader–Willi syndrome

Merlin G. Butler[1] · **A. Kaitlyn Victor**[2,3] · **Lawrence T. Reiter**[2,4]

Received: 26 September 2022 / Accepted: 14 November 2022 / Published online: 14 December 2022

Abstract

Introduction Prader–Willi syndrome is a complex neurodevelopmental genetic disorder due to lack of paternal expression of critical imprinted genes in the 15q11.2-q13.1 chromosomal region, generally from a paternal deletion. Predominant features include infantile hypotonia, a poor suck with failure to thrive, craniofacial features, and developmental and behavioral problems including self-injury and childhood onset of obesity. In addition to severe obesity, patients with PWS present with other symptoms of autonomic nervous system dysfunction.

Methods We examined the features seen in Prader–Willi syndrome and searched the literature for evidence of autonomic nervous system involvement in this rare obesity-related disorder and illustrative findings possibly due to autonomic nervous system dysfunction. Additionally, we reviewed the literature in relation to childhood obesity syndromes and compared those syndromes to the syndromic obesity found in Prader–Willi syndrome.

Results We report autonomic nervous system-related symptoms associated with childhood obesity impacting features seen in Prader–Willi syndrome and possibly other obesity-related genetic syndromes. We compiled evidence of both an autonomic route for the obesity seen in PWS and other autonomic nervous system-related dysfunctions. These include decreased salvation, sleep disordered breathing, increased pain and thermal threshold instability, delayed gastric emptying, altered blood pressure readings, and pupillary constriction responses as evidence of autonomic nervous system involvement.

Conclusions We summarized and illustrated findings of autonomic nervous system dysfunction in Prader–Willi syndrome and other obesity-related syndromes and genetic factors that may play a causative role in development.

Keywords Prader–Willi syndrome · Obesity · Autonomic nervous system dysfunction · Neurodevelopment

Introduction

Prader–Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder caused by errors in genomic imprinting of the 15q11.2-q13.1 region. PWS affects approximately 1:10,000–30,000 individuals with an estimated 350,000–400,000 cases worldwide [1–5]. Features of PWS include severe hypotonia with a poor suck and failure to thrive during infancy with hypogonadism and hypogenitalism noted in both sexes. Additional presentations include developmental delay, facial dysmorphology (bifrontal narrowing, upslanting, almond-shaped eyes, high palate, small chin), short stature, small hands and feet, as well as growth and other hormone deficiencies with endocrine dysfunction involving the thyroid, sex organs, pancreas, and adrenal glands [5, 6]. Several of these endocrine disturbances can be seen during infancy, childhood, or adolescence, including hypothyroidism, adrenal insufficiency, and hypogonadism with altered pubertal development [7]. Swallowing difficulties and a poor suck reflex are common during infancy; however, in early childhood and into adulthood, the patients display excessive eating with hyperphagia and poor satiety, decreased physical activity, and lower resting metabolism that leads to severe obesity if not externally controlled. Hyperphagia is a major problem in PWS and typically lasts

✉ Merlin G. Butler
mbutler4@kumc.edu

[1] Departments of Psychiatry & Behavioral Sciences and Pediatrics, University of Kansas Medical Center, Kansas City, KS 66160, USA

[2] Department of Neurology, The University of Tennessee Health Science Center, Memphis, TN 38163, USA

[3] IPBS Program, The University of Tennessee Health Science Center, Memphis, TN 38163, USA

[4] Department of Pediatrics and Anatomy & Neurobiology, The University of Tennessee Health Science Center, Memphis, TN 38163, USA

over the lifetime with no known treatment options once it develops. Mild intellectual disabilities and associated psychiatric manifestations are present including addictive behaviors, obsessive compulsive disorders, attention deficit hyperactivity, violent outbursts, poor peer interactions, stubbornness, and skin picking with evidence of eating nonfood or inedible items [5, 6, 8–10]. These patterns can continue into adolescence and adulthood.

Genetic basis of PWS

Individuals with PWS show lack of expression of imprinted genes from the paternally expressed 15q11.2-q13.1 chromosome region and are grouped into three molecular genetic classes. These include a common paternal 15q11.2-q13.1 deletion, generally sporadic in origin, seen in approximately 60% of individuals with PWS, followed by maternal disomy 15 seen in approximately 35% of cases. Most of the remaining subjects have a defect in the imprinting center that controls the activity of imprinted genes on chromosome 15 or other chromosome 15 abnormalities including translocations and inversions [2, 11–13]. Reported clinical differences in those PWS individuals with the chromosome 15q11.2-q13.1 deletion include hypopigmentation and greater clinical homogeneity [14–16]. Those with maternal disomy 15 are at an increased risk of developing psychiatric disorders and behavioral problems including autism and cycloid psychosis [17–23].

There are two typical deletion subtypes of the 15q11.2-q13.1 deletion (larger type I and smaller type II) involving two proximal 15q11.2 breakpoints (BP1 seen in type I and BP2 seen in type II) but the same distal breakpoint (BP3) in both deletion subtypes. There are four genes in the 15q11.2 BP1 and BP2 region (*NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*) that code for magnesium transporters, axon growth, neurodevelopmental and bone morphogenic proteins known to impact brain function and bone with cartilage development. When these genes are deleted only, they play a role in an emerging disorder [15q11.2 BP1-BP2 deletion or Burnside–Butler syndrome], which is a separate condition with motor and speech delay, mood disorders and neurobehavioral problems including autism and seizures [24–26]. Hence, the individuals with PWS containing the larger type I deletion, with the four genes deleted, are more prone to severe clinical findings including lower functioning, increased skin picking and compulsions than those with the smaller type II deletion, where the four BP1-BP2 located genes are intact.

Individuals with PWS caused by maternal disomy 15 (or both chromosome 15s from the mother), due to nondisjunction during female meiosis or gamete production, can be grouped into three subclasses (maternal heterodisomy, maternal segmental isodisomy, or maternal total isodisomy). Those with maternal heterodisomy have both chromosome 15s from the mother without crossover events which normally occur in maternal meiosis I; therefore, the genetic pattern of each of the 15s found in the egg remain different while those with segmental isodisomy will have the same or identical chromosome 15 segments due to crossover events in meiosis. Those with total isodisomy of the entire chromosome 15 will have identical DNA patterns on each of the 15s. Hence, if the mother is a carrier of a recessive gene that causes disease, of which there are dozens on chromosome 15, then the child will have PWS due to two 15s from the mother and a second genetic condition (e.g., Bloom syndrome) due to a homozygous mutation on chromosome 15. This is important for genetic counseling and management of the PWS child for additional genetic conditions if the gene is located in the isodisomic region or for the entire chromosome 15 with many potential at risk disease-causing genes. These PWS children should then be followed for PWS and under-surveillance for other recessive disorders on chromosome 15, if needed [5].

Autonomic system dysfunction in PWS

Individuals with PWS present with varying degrees of autonomic nervous system (ANS) dysfunction. Figure 1 shows these affected systems and characteristics. PWS subjects have thermal regulation problems resulting in hypo- or hyperthermia with reduction in core temperature in response to cold stress, decreased pain sensation with self-injury, gastrointestinal disturbances involving the oropharyngeal region and bowel motility characterized by increased prevalence of prolonged total gastrointestinal transit time and delayed gastric emptying with decreased salivation and altered sleep control with excessive daytime somnolence [27, 28]. Several of these findings represent an abnormality in circadian rhythm and rapid eye movement sleep, insensitivity to hypoxia and hypercarbia, pain perception with learning, and behavior problems along with poor executive planning [27]. Some features seen in PWS are similarly seen in patients with classic peripheral ANS disorders such as familial dysautonomia, a recessive genetic condition caused by mutations of the *IKBKAP* gene affecting the development, migration, and survival of sensory and autonomic neurons [29]. These features include sleep-disordered breathing and reduced or inappropriate responses to hypoxia and hypercapnia [30, 31].

DiMario et al. evaluated 14 subjects with PWS and a similar number of controls from 4 to 40 years of age using anthropometric measurements, body mass index (BMI), and simultaneous and serial electrocardiograms (ECGs) with recordings of pulse rate and blood pressure, plasma norepinephrine levels at rest after standing, and eye pupillary

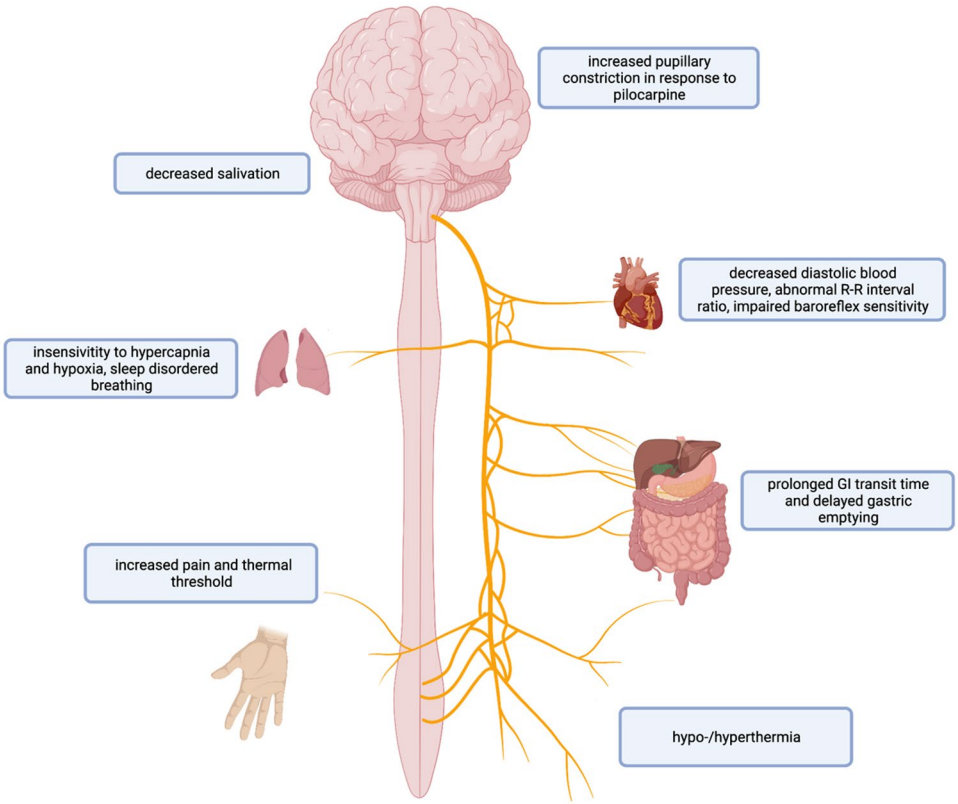

Fig. 1 Autonomic nervous system dysfunction in Prader–Willi syndrome. Created with BioRender.com

responses [8]. These assessments were done to monitor the function of the ANS, both parasympathetic and sympathetic. They observed abnormal findings in subjects with PWS including a trend of lower resting diastolic blood pressure and less change in diastolic blood pressure after standing. The PWS subjects had greater BMI measurements than control subjects, which correlated significantly with all pulse-rate measurements. Additionally, they found that those with greater BMI measures had higher pulse rates at rest. The pupillary constrictions to dilute pilocarpine were also found in 50% of the PWS subjects and in no control subjects. The R-R interval ratio in ECGs were abnormal in 40% of the PWS subjects and in no controls. They concluded that their results suggested that patients with PWS have a detectable underlying ANS dysfunction characterized principally by diminished parasympathetic nervous system activity. Later, Kaur et al. reported an adult male with PWS undergoing a battery of tests to assess vascular structure and function and baroreflex sensitivity, blood pressure variability and autonomic tone along with autonomic reactivity tests [32]. They observed impaired baroreflex sensitivity along with orthostatic tachycardia with normal vascular function tests and concluded that their patient with PWS showed baroreflex dysfunction with probable afferent and/or central autonomic neural defects. In another study of 40 PWS patients, Bray et al. found that, when compared to obese control subjects, PWS subjects had disrupted body temperature regulation and reduced salivary secretion [33]. Priano et al. observed increased thermal and pain thresholds in PWS subjects when compared to both healthy and obese subjects [28].

In addition to the above symptoms of ANS dysfunction, severe obesity beginning in childhood is a hallmark of PWS. ANS dysfunction has been implicated in various forms of childhood obesity [34–36]. The ANS is divided into two systems with opposing states (sympathetic or stimulation and parasympathetic or inhibition). Disturbed regulation of either the parasympathetic or sympathetic branches in the ANS, or both, may contribute to development of obesity and related metabolic comorbidities associated with obesity-related disorders such as PWS [33, 37]. Low sympathetic activity could predispose to increased weight with decreased energy expenditure while a decrease in parasympathetic function may be associated with comorbid development with altered regulation of food intake and satiety; important contributors to onset, development, and progression of obesity status [27, 38]. There are several nutritional phases of the PWS clinical course starting with feeding difficulties due to hypotonia in infancy followed by a transition to increased weight gain with or without increased caloric intake. In the final stages, food seeking, driven by hyperphagia, leads to severe obesity in early childhood and continues into adulthood [5]. The complications that arise from this severe obesity decrease the life expectancy and quality of PWS subjects [10].

PWS-driven obesity differs in several ways from non-syndromic obesity. Figure 2 shows a PWS patient with the classic PWS obesity phenotype. PWS subjects have lower lean body mass compared to obese subjects and reduced resting energy expenditure [39]. Additionally, PWS subjects typically have excessive fat mass in the trunk and proximal extremity of the limbs, which differs from the distribution of fat mass in non-syndromic obese individuals [39]. PWS individuals also appear to have increased insulin sensitivity and decreased levels of visceral fat and pro-inflammatory adipokines when compared to obese control subjects [40–42].

Relationship to obesity-related genes and syndromes

Over 500 obesity-related genes have been identified [43]. These genes play a role in appetite regulation and control, body composition and fat distribution patterns, metabolic regulation and energy expenditure, and storage and utilization [5, 10, 43]. The current obesity epidemic worldwide can be attributed to a complex interaction between genetic and environmental factors including gene function, protein pathways, and biological processes. There are limited examples in humans of obesity-related genetic disorders with marked early onset of severe or life-threatening obesity. PWS is a classic example of this obesity type. Gabrielli et al. used genome functional pathway analysis and found 46 disturbed pathways, 62 biological processes, 22 molecular functions, and 148 phenotypes that impact adipogenesis, signal transductions related to G-protein coupled receptors, and lipid metabolism involving insulin-related genes [44]. Biological processes identified included feeding behavior, cholesterol metabolism, and glucose with cholesterol homeostasis pathways. Molecular processes pertained to receptor binding, which affects glucose homeostasis, body weight, and circulating insulin and triglyceride levels [44].

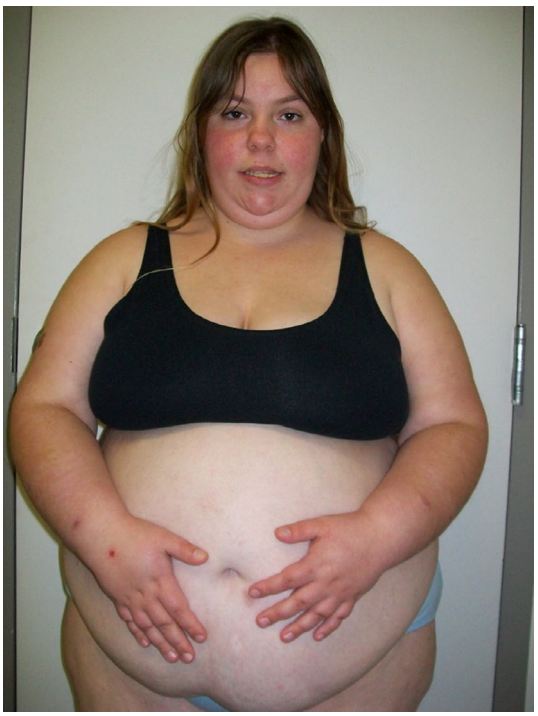

Fig. 2 Frontal view of a 16-year-old female with Prader–Willi syndrome due to maternal disomy 15 showing typical craniofacial findings, central obesity, and self-injury sites common in this genetic obesity-related disorder

There are over 30 recognized syndromes with obesity as a major manifestation. Currently, several dozen other obesity-related disorders are understudied or undercharacterized [5, 43]. Genetic obesity disorders have clinical features that overlap with 52 known obesity syndromes that display intellectual disability. Seven of these syndromes present with macrocephaly and seven syndromes with microcephaly [45]. These syndromes exhibit complex forms of inheritance such as autosomal dominant, autosomal recessive, X-linked (e.g., Börjeson–Forssman–Lehmann), genomic imprinting errors (e.g., PWS), triallelic inheritance (e.g., Bardet–Biedel), triplet repeat expansion (e.g., fragile X) or chromosomal anomalies (e.g., 16p11.2 deletion) [5].

There is now a growing interest in an emerging disorder with rapid onset of obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) evolving over time. This condition was first described over 50 years ago [46] and now there are fewer than 200 reported cases [47] with an abrupt onset of extreme weight gain and an unreported genetic cause but with a partially overlapping natural history in those with PWS. Reports of those with ROHHAD have now been described to further characterize the spectrum of clinical manifestations, specifically rapid-onset obesity (weight gain of 20–30 pounds over a 3–12-month interval) between 2 to 7 years in a previously healthy child with normal neurocognitive development [48]. Compared to the onset of obesity in children with PWS, children with ROHHAD show steeper growth curves [47]. Alveolar hypoventilation typically begins after weight gain and within 1 to 2 years [47]. Hypothalamic and/or pituitary hormone dysfunction is noted along with possible growth hormone deficiency, central hypothyroidism, diabetes insipidus, adrenal insufficiency hyperprolactinemia, and pubertal disturbances. In addition, autonomic dysregulation and neuroendocrine tumors are present [47–50]. Autonomic dysregulation may include ophthalmologic manifestations (altered pupillary response to light and strabismus), thermal dysregulation, gastrointestinal dysmotility, altered vasomotor tone, an elevated pain threshold but without increased pain cardiovascular involvement including bradycardia, and neural crest tumors. Worsening or mismanagement of

hypoventilation can result in impaired neurocognitive development and/or cardiorespiratory arrest in those affected [47].

The identification of overlapping clinical manifestations between ROHHAD and PWS has stimulated molecular genetic testing to identify genetic causes of those meeting the clinical criteria of ROHHAD using genes contributing to features of PWS such as *MAGEL2* or other genes known to cause obesity-related syndromes including the *RAI1* gene causing Smith–Magenis syndrome [43]. Barclay et al. performed molecular genetic testing of imprinted genes in the PWS chromosome 15q11.2-q13.1 region, but no disease-causing mutations were found in the PWS candidate genes [47]. However, more genetic testing should be undertaken using advanced genetic testing with whole exome next-generation sequencing in those meeting the criteria for ROHHAD as currently over 120 obesity-related genes are now available in obesity gene panels from commercial genetic testing laboratories [43].

Conclusions

The pathogenesis of obesity is complex, with many underlying contributing factors with evidence that progression of obesity in children and adults may be linked to dysregulation between the central nervous system and ANS, with involvement of the peripheral endocrine system including fat mass and regulation of appetite control and the gastrointestinal tract [27, 51]. The ANS involves control of important functions related to breathing, heart rate, blood pressure, body temperature, appetite, and digestion with hormone production regulating distribution of body fat and development of related comorbidities. Understanding associated morbid obesity and contributing factors in those individuals with genetic causes of marked obesity or syndromes, such as PWS, may impact therapeutic targets and interventions with medical devices [27].

Adult studies in obesity and ANS dysfunction might not be appropriate or accurate as pathogenic mechanisms that are present in childhood may be confounded by the effects of advancing age and age-related disease. The progression of obesity in adults is often associated with adaptive increase in sympathetic activity that may contribute to the development of obesity-related complications such as high blood pressure and associated increased weight compared to children [27]. In addition, genes involved in or contributing to obesity in humans would indicate the presence of 500 recognized genes, about 20% of which are noted to play a role in pediatric onset of obesity [43]. Further studies are warranted in the involvement of the ANS and its role in onset and progression of obesity to better understand their important contributions in the regulation and development of body fat and distribution including comorbidities, which may ultimately guide novel obesity therapeutics targeting specific ANS dysfunction disturbed in PWS.

Acknowledgements MGB acknowledges support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Grant #02528. LTR acknowledges support from the Foundation for Prader–Willi Research.

Funding Eunice Kennedy Shriver National Institute of Child Health and Human Development, HD02528, Merlin G. Butler. Foundation for Prader–Willi Research, Lawrence T. Reiter.

Data availability statement All data in this review have been previously published and is part of the public record.

Declarations

Conflict of interest The authors declare no competing interests related to this work. On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Butler MG, Thompson T (2000) Prader–Willi syndrome: clinical and genetic findings. Endocrinologist 10(4 Suppl 1):3s–16s
2. Bittel DC, Butler MG (2005) Prader–Willi syndrome: clinical genetics, cytogenetics and molecular biology. Expert Rev Mol Med 7(14):1–20
3. Cassidy SB, Driscoll DJ (2009) Prader–Willi syndrome. Eur J Hum Genet 17(1):3–13
4. Cassidy SB et al (2012) Prader–Willi syndrome. Genet Med 14(1):10–26
5. Butler MG (2016) Single gene and syndromic causes of obesity: illustrative examples. Prog Mol Biol Transl Sci 140:1–45
6. Butler MG (2006) Management of obesity in Prader–Willi syndrome. Nat Clin Pract Endocrinol Metab 2(11):592–593
7. Angulo MA, Butler MG, Cataletto ME (2015) Prader–Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Invest 38(12):1249–1263
8. DiMario FJ Jr et al (1994) An evaluation of autonomic nervous system function in patients with Prader–Willi syndrome. Pediatrics 93(1):76–81
9. Symons FJ et al (1999) Self-injurious behavior and Prader–Willi syndrome: behavioral forms and body locations. Am J Ment Retard 104(3):260–269
10. Butler MG (2011) Prader–Willi syndrome: obesity due to genomic imprinting. Curr Genomics 12(3):204–215
11. Butler MG et al (2019) Molecular genetic classification in Prader–Willi syndrome: a multisite cohort study. J Med Genet 56(3):149–153
12. Butler MG, Duis J (2020) Chromosome 15 imprinting disorders: genetic laboratory methodology and approaches. Front Pediatr 8:154
13. Strom SP et al (2021) A streamlined approach to Prader–Willi and Angelman syndrome molecular diagnostics. Front Genet 12:608889
14. Butler MG, Meaney FJ, Palmer CG (1986) Clinical and cytogenetic survey of 39 individuals with Prader–Labhart–Willi syndrome. Am J Med Genet 23(3):793–809
15. Butler MG (1989) Hypopigmentation: a common feature of Prader–Labhart–Willi syndrome. Am J Hum Genet 45(1):140–146

16. Butler MG (1990) Prader–Willi syndrome: current understanding of cause and diagnosis. Am J Med Genet 35(3):319–332
17. Victor AK et al (2021) Molecular changes in Prader–Willi syndrome neurons reveals clues about increased autism susceptibility. Front Mol Neurosci 14:747855
18. Whittington J, Holland A (2010) Neurobehavioral phenotype in Prader–Willi syndrome. Am J Med Genet C Semin Med Genet 154c(4):438–447
19. Bennett JA et al (2015) Autism spectrum disorder in Prader–Willi syndrome: a systematic review. Am J Med Genet 167A:2936–2944
20. Dykens EM et al (2017) Diagnoses and characteristics of autism spectrum disorders in children with Prader–Willi syndrome. J Neurodev Disord 9:18
21. Dimitropoulos A, Zyga O, Russ SW (2019) Early social cognitive ability in preschoolers with Prader–Willi syndrome and autism spectrum disorder. J Autism Dev Disord 49(11):4441–4454
22. Verhoeven WM, Tuinier S, Curfs LM (2003) Prader–Willi syndrome: cycloid psychosis in a genetic subtype? Acta Neuropsychiatr 15(1):32–37
23. Singh D et al (2019) Cycloid psychosis comorbid with Prader–Willi syndrome: a case series. Am J Med Genet A 179(7):1241–1245
24. Butler MG (2017) Clinical and genetic aspects of the 15q11.2 BP1-BP2 microdeletion disorder. J Intellect Disabil Res 61(6):568–579
25. Rafi SK, Butler MG (2020) The 15q11.2 BP1-BP2 microdeletion (Burnside-Butler) syndrome: in silico analyses of the four coding genes reveal functional associations with neurodevelopmental phenotypes. Int J Mol Sci 21(9):3296–3332
26. Baldwin I et al (2021) Genomic, clinical, and behavioral characterization of 15q11.2 BP1-BP2 deletion (Burnside-Butler) syndrome in five families. Int J Mol Sci 22(4):1660–1684
27. Haqq AM et al (2011) Autonomic nervous system dysfunction in obesity and Prader–Willi syndrome: current evidence and implications for future obesity therapies. Clin Obes 1(4–6):175–183
28. Priano L et al (2009) On the origin of sensory impairment and altered pain perception in Prader–Willi syndrome: a neurophysiological study. Eur J Pain 13(8):829–835
29. Cuajungco MP et al (2001) Cloning, characterization, and genomic structure of the mouse Ikbkap gene. DNA Cell Biol 20(9):579–586
30. Palma JA et al (2019) Chemoreflex failure and sleep-disordered breathing in familial dysautonomia: implications for sudden death during sleep. Auton Neurosci 218:10–15
31. Gillett ES, Perez IA (2016) Disorders of sleep and ventilatory control in Prader–Willi syndrome. Diseases 4(3):23
32. Kaur M et al (2016) Baroreflex dysfunction in Prader–Willi syndrome. J Clin Diagn Res 10(3):Cd01-2
33. Bray GA et al (1983) The Prader–Willi syndrome: a study of 40 patients and a review of the literature. Medicine (Baltimore) 62(2):59–80
34. Baum P et al (2013) Dysfunction of autonomic nervous system in childhood obesity: a cross-sectional study. PLoS ONE 8(1):e54546
35. Nagai N et al (2003) Autonomic nervous system activity and the state and development of obesity in Japanese school children. Obes Res 11(1):25–32
36. Yakinci C et al (2000) Autonomic nervous system functions in obese children. Brain Dev 22(3):151–153
37. Bray GA, York DA (1979) Hypothalamic and genetic obesity in experimental animals: an autonomic and endocrine hypothesis. Physiol Rev 59(3):719–809
38. Smith PH, Madson KL (1981) Interactions between autonomic nerves and endocrine cells of the gastroenteropancreatic system. Diabetologia 20(Suppl):314–324
39. Crinò A et al (2018) Obesity management in Prader–Willi syndrome: current perspectives. Diabetes Metab Syndr Obes 11:579–593
40. Irizarry KA et al (2016) Prader–Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. Adv Pediatr 63(1):47–77
41. Haqq AM et al (2007) Altered distribution of adiponectin isoforms in children with Prader–Willi syndrome (PWS): association with insulin sensitivity and circulating satiety peptide hormones. Clin Endocrinol (Oxf) 67(6):944–951
42. Goldstone AP et al (2001) Visceral adipose tissue and metabolic complications of obesity are reduced in Prader–Willi syndrome female adults: evidence for novel influences on body fat distribution. J Clin Endocrinol Metab 86(9):4330–4338
43. Duis J, Butler MG (2022) Syndromic and Nonsyndromic Obesity: Underlying Genetic Causes in Humans. Adv Biol (Weinh) 6(10):e2101154
44. Gabrielli AP, Manzardo AM, Butler MG (2017) Exploring genetic susceptibility to obesity through genome functional pathway analysis. Obesity (Silver Spring) 25(6):1136–1143
45. Kaur Y et al (2017) A systematic review of genetic syndromes with obesity. Obes Rev 18(6):603–634
46. Fishman LS, Samson JH, Sperling DR (1965) Primary alveolar hypoventilation syndrome (Ondine's Curse). Am J Dis Child 110:155–161
47. Barclay SF et al (2018) ROHHAD and Prader–Willi syndrome (PWS): clinical and genetic comparison. Orphanet J Rare Dis 13(1):124
48. Ize-Ludlow D et al (2007) Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. Pediatrics 120(1):e179–e188
49. Abaci A et al (2013) A case of rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation, and neural crest tumor: ROHHADNET syndrome. Endocr Pract 19(1):e12–e16
50. Rand CM et al (2011) Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: analysis of hypothalamic and autonomic candidate genes. Pediatr Res 70(4):375–378
51. Zac-Varghese S, Tan T, Bloom SR (2010) Hormonal interactions between gut and brain. Discov Med 10(55):543–552