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Case Report

Management of Life-Threatening Obesity and Type 2 Diabetes Mellitus in Prader-Willi Syndrome Using a Combination Therapy of Semaglutide and Methylphenidate

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Abstract

Objective: Hyperphagia, subsequent obesity and its complications are among the major treatment challenges in Prader-Willi syndrome (PWS) as hyperphagia is observed in all genetic subgroups. Hyperphagia has a significant impact on the quality of life of the person with PWS and caregivers as it requires a lifelong and stringent diet plan. Despite numerous options in the armamentarium for the treatment of hyperphagia, obesity, and Type 2 diabetes mellitus (T2DM) in PWS, achieving weight loss is extremely difficult. We were successful in achieving significant weight loss, complete resolution of T2DM, and improvement in food-related behaviors using Semaglutide and Methylphenidate combination therapy in a child with PWS. Our patient achieved a weight loss of 5% in a period of 4 weeks then a further 8.4% in 11 weeks and a 11.5% reduction in 18 weeks during the duration of treatment, all of which are significant. This combination therapy has resulted in a dramatic and lifesaving reduction in weight and complete resolution of T2DM in our patient.

Keywords: Obesity; Hyperphagia; Semaglutide; Methylphenidate; Prader-Willi syndrome (PWS)

Introduction

Prader-Willi syndrome (PWS) is a genetic, rare multisystemic, neurodevelopmental disorder characterized by impaired hypothalamic function due to abnormal DNA methylation within the region of 15q11.2-q13. The incidence of PWS is approximately 1 in 16,000 to 1 in 21,000 live births [1]. Hyperphagia is a major treatment challenge in PWS and is observed in all genetic subgroups, however more frequently encountered in patients with deletion. The genetic defects in the 15q11-q13 region often include microdeletions of the paternally expressed non-coding snoRNAs such as SNORD115 and SNORD116. Some of animal studies have shown that mice with disturbances of SNORD116 equivalent transcripts exhibit hyperphagia and growth failure [2]. It has a significant impact on the quality of life of the person with PWS and caregivers as it requires a lifelong, stringent diet plan [1]. Hyperphagia and obesity in PWS are postulated to be caused by a combination of hypothalamic dysfunction, hormonal circuits involved in satiety control, changes in body composition, and decreased resting energy expenditure [3]. The pharmacotherapy options that have been reported for the treatment of hyperphagia and obesity in PWS include Phentermine, Topiramate, Glucagon-like peptide 1 receptor (GLP-1) agonist (Exenatide, Liraglutide), Naltrexone-

Bupropion, newer drugs such as Setmelanotide, Oxytocin, Diazoxide and Unacylated ghrelin analog [4]. Some case reports and clinical trials have reported that treatment with a GLP-1 agonist, such as Exenatide or Liraglutide had beneficial effects on obesity, satiety, and glycemic control in PWS patients however these were not significant. The failure of Liraglutide to reduce body mass index (BMI) significantly is not completely understood but may be related to the underlying hypothalamic dysregulation of PWS, which may hinder the effect of Liraglutide on appetite centers in the hypothalamus [5]. Most of the above-mentioned treatment options have been ineffective and some have been withdrawn from the market due to the adverse effects. Early initiation of growth hormone (GH) treatment increases muscle mass and reduces BMI in PWS but is ineffective at controlling the hyperphagia as most of the PWS patients who have been treated with GH still remain obese. Hence, achieving weight loss in PWS is extremely difficult. Here we report our experience of using a combination therapy of Semaglutide and Methylphenidate in a child with PWS to achieve a significant weight loss, complete resolution of Type 2 diabetes mellitus (T2DM) and improvement in food- seeking behaviors.

Case Presentation

A 9.5-year-old girl with PWS was referred to our center for the management of severe obesity with multiple co-morbidities. She had been to multiple centers around the world for the same. She was the 3rd child of non-consanguineous parents who was diagnosed with PWS at the age of 2 years due to paternal 15q microdeletion. The onset of polyphagia and rapid weight gain started at the age of 4 years. The severe co-morbidities that the child had at the time of consultation at our center were hypoventilation syndrome with severe obstructive sleep apnea and chronic respiratory failure requiring overnight BiPAP and oxygen during the day, T2DM since the age of 7 years requiring basal-bolus insulin regimen, Metformin 2 grams per day and fatty liver. The management of her severe obesity at the other centers till the consultation at our center included lifestyle modification, various forms of low-calorie diets and laparoscopic sleeve gastrectomy at a BMI of 80kg/m2 done at the age of 7 years of age. However, there was less than 5kg reduction. She was initiated on GH at the referring center at the age of 5 years, however had to be discontinued due to worsening sleep apnea. On presentation to our center, the child had a weight of 149kg (100th centile, 4.4 standard deviation score), height 140cm (75th centile, mid-parental height between 90-95th centile), BMI 76.8kg/m^2 (99th centile). She had symptomatic worsening of the apnea.

Therapeutic intervention: At our center, she was initiated on Semaglutide 1mg weekly and Methylphenidate 18mg once daily for control of hyperphagia and weight reduction. She was being continued on basal insulin and initiated on bolus insulin for meals and snacks as per carbohydrate counting. The doses of Semaglutide and Methylphenidate were increased as shown in (Figure 1).

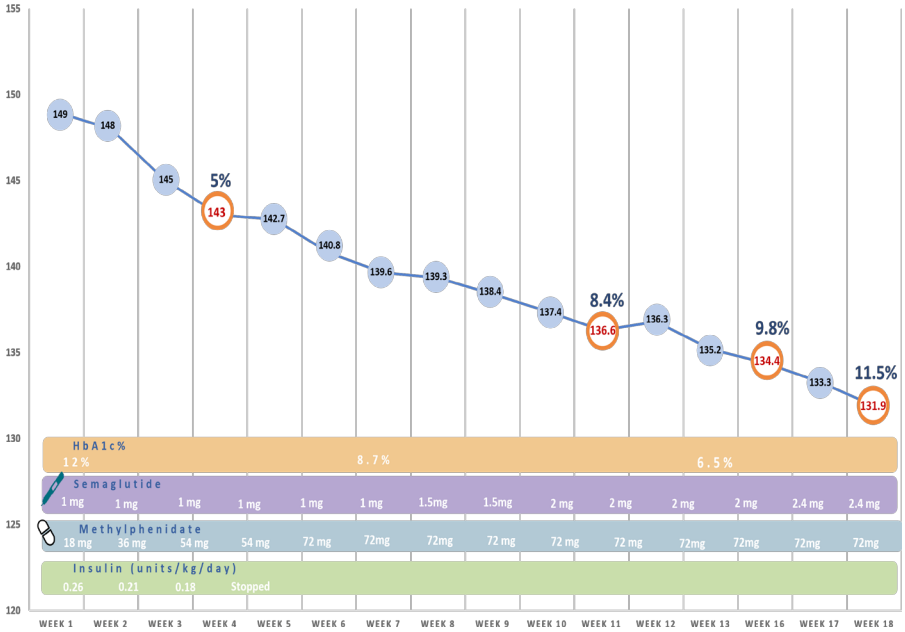

Figure 1: Increasing doses of Semaglutide and Methylphenidate.

Results

By the end of 18 doses of Semaglutide and Methylphenidate, there was 11.5% reduction in body weight and she had reduced appetite. The basal insulin dose was gradually tapered down after 10 days of treatment initiation with Semaglutide and Methylphenidate and the basal and bolus insulin could be stopped within 4 weeks of treatment initiation at our center. She had symptomatic improvement in sleep apnea by week 6 of combination therapy. She was able to be off oxygen during the daytime naps. At week 18 the follow-up sleep study showed acceptable sleep efficiency with good sleep architecture. Some of the challenges observed with following the lifestyle modifications initiated were, initially insisting on using the wheelchair to mobilize when she was medically fit to independently walk, consuming high calorie/ sugar snacks when out on hospital pass, consuming high calorie/ sugar snacks from family and sharing the care giver's meal tray despite multiple sessions with the diabetes dietitians for encouragement and adherence to healthy eating habits.

Discussion

This is the first case in this age group reporting the use of a combination therapy of Semaglutide and Methylphenidate to treat hyperphagia, obesity and T2DM in a PWS patient. This combination therapy has resulted in a dramatic and lifesaving reduction in weight and complete resolution of T2DM in our patient. It is possible that the combination of daily Methylphenidate and weekly Semaglutide are acting synergistically as previous reports of using Liraglutide only in PWS patients did not report any significant weight loss[5]. Methylphenidate increases dopamine levels within the neuronal synapses by selectively binding to the dopamine transporter leading to decreased dopamine reuptake. Dopamine is a potent inhibitor of feeding as it inhibits the expression of neuropeptide Y, an orexigenic peptide [6]. Hence Methylphenidate suppresses appetite. Semaglutide reduces food intake and affects satiety centrally by signaling through GLP-1 receptors in the arcuate nucleus of the hypothalamus and like dopamine directly inhibits neuropeptide Y [7]. GLP-1 receptors are present in the hypothalamus, brainstem, and nuclei of the mesolimbic system and these are the key areas that control energy balance. GLP-1 agonists suppress the desire for food intake by interacting with these key areas. The peripheral administration of GLP-RA causes it to reach the hindbrain via circulation or vagal afferents. The anorectic effect of exogenous GLP-1 is impaired in rodents with vagotomy which suggests that the vagal-brainstem-hypothalamic pathway plays a role in its effects on food intake [8]

Conclusion

A 5% weight loss from baseline is considered as a clinically meaningful amount [9]. Our patient went on to have weight loss of 5% in a period of 4 weeks and further 8.4% in 11weeks, 11.5% reduction in 18 weeks during her duration of treatment, all of which are significant. There was complete resolution of T2DM and significant improvement in hyperphagia and food seeking behavior. Hence combination therapy of Semaglutide and Methylphenidate may be useful in other patients with PWS but warrants further clinical trials.

Takeaway lessons: The anorectic potency of the combination of Semaglutide and Methylphenidate can be effectively utilized in PWS. Significant weight loss can have game-changing effects on metabolic complications such as T2DM and severe obstructive sleep apnea in PWS. Combination therapy with Semaglutide and Methylphenidate can reduce the need for bariatric surgery in PWS.

Contributors: All authors made individual contributions to authorship. Khalid Hussain was involved in treatment selection, follow-up, and manuscript preparation. Shiga Chirayath was involved in the treatment, manuscript preparation, and submission. Hajar Dauleh was involved in the follow-up during treatment. Maheen Pasha and Fatima Ismail were involved in the nutritional management. All authors reviewed and approved the final draft.

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