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CASE REPORT

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Weight loss with glucagon-like peptide-1 receptor agonists in Bardet-Biedl syndrome

Shawg Ganawa[1] | Smrithi Hema Santhosh[1,2] | Lucy Parry[1,3] | Akheel A. Syed[1,4]

[1]Diabetes, Endocrinology and Obesity Medicine, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK

[2]Undergraduate Medical Education, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK

[3]School of Medical Sciences, University of Manchester, Manchester, UK

[4]Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, Manchester, UK

Correspondence
Akheel A. Syed, Department of Diabetes, Endocrinology and Obesity Medicine, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK.
Email: akheel.syed@manchester.ac.uk

Summary

Bardet–Biedl syndrome (BBS) is a rare genetic condition, characterized by ciliary protein dysfunction, leading to multi-organ damage. People with BBS can develop early-onset severe obesity and associated problems including the metabolic syndrome, type 2 diabetes and coronary heart disease. Weight management can be challenging with the lack of effective medical therapies so far. We report a patient with BBS who underwent successful weight reduction through the use of glucagon-like peptide-1 receptor agonists.

KEYWORDS

Type 2 diabetes mellitus, glucagon-like peptide-1, hypothalamic diseases, incretins, Laurence-Moon–Bardet-Biedl syndrome, morbid obesity, weight loss

What is already known about this subject

- Bardet–Biedl syndrome (BBS) is a rare genetic condition associated with severe obesity from a young age.
- The options of weight management are limited, and efficacy of pharmacotherapy is unknown.

What this study adds

- We show significant weight reduction with lifestyle and dietary management alongside glucagon-like peptide-1 receptor agonist treatment in a young woman with BBS.
- Weight loss pharmacotherapy is a promising avenue of treatment in genetic obesity syndromes with several novel molecules on the horizon.

A 28-year-old woman was referred to our specialized complex obesity service with childhood-onset obesity associated with hyperphagia. She also had longstanding retinitis pigmentosa, acanthosis nigricans, polycystic ovarian syndrome, hypothyroidism and hypertension and recent-onset type 2 diabetes. Her body mass index (BMI) was 37.9 kg/m^2. There was no polydactyly. She was studying at university. She was taking metformin, ramipril and levothyroxine. A clinical diagnosis of Bardet–Biedl syndrome (BBS) was suspected, and genetic testing by Sanger sequencing confirmed homozygous c.1599_1602del p. (Thr53411efs*21) in the BBS10 gene (12q21.2).

Initial management was focused on weight reduction with lifestyle and dietary management. A dietary history established that there was a high intake of fizzy drinks, large portion sizes and mealtimes out of keeping with the norm. Changes included moving forward mealtimes, eating smaller portion sizes, eating foods with a low glycaemic index and removing fizzy drinks from the diet. She had

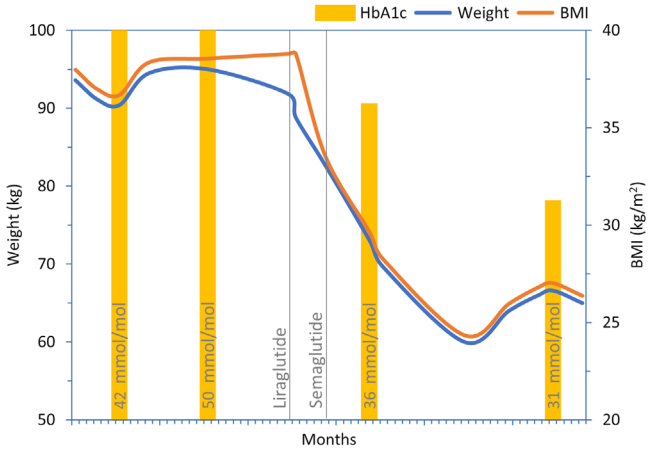

FIGURE 1 Clinical course of weight management in a patient with Bardet–Biedl syndrome. Weight (kg) depicted by blue trace, body mass index (BMI, kg/m^2) by orange trace and glycated haemoglobin (HbA1c, mmol/mol) by yellow columns. Initial weight reduction with the sodium-glucose co-transporter-2 inhibitor, Canagliflozin, was short-lived and poorly tolerated. Treatment with glucagon-like peptide-1 receptor agonists (daily liraglutide initially, later replaced with weekly semaglutide, depicted by grey droplines) resulted in total weight loss of 33% and normalization of glycated haemoglobin. Lifestyle and dietary management and semaglutide therapy continue for long-term weight maintenance

previously tried weight loss medications including orlistat, sibutramine and rimonabant with no lasting benefit. Adjunctive pharmacotherapy with the sodium-glucose cotransporter-2 (SGLT2) inhibitor, Canagliflozin, led to modest weight loss that was short-lived; it was not tolerated due to perineal thrush. She was subsequently commenced on daily injections of the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide (up to 1.8 mg daily), resulting in significant weight loss over a 5-month period with reduction in BMI to 33.5 kg/m^2 (Figure 1). Liraglutide was later replaced with semaglutide injections for the convenience of weekly dosing as per patient's preference. Following 19 months of treatment with semaglutide (up to 1 mg weekly), there was further significant weight loss, achieving a nadir BMI of 24.3 kg/m^2. As there was some weight regain upon dose reduction of semaglutide, a maintenance dose of semaglutide (1 mg weekly) and metformin (500 mg twice daily) have been continued with good weight control and glycaemic control.

1 | DISCUSSION

Bardet–Biedl syndrome (BBS), a pleiotropic autosomal recessive disorder affecting ciliary protein function,[1] is caused by biallelic loss-of-function pathogenic variants in one of at least 26 genes,[2] and is characterized by retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties and hypogonadism.[3] Prevalence varies geographically with an estimated incidence of 1 in 160 000 new-borns in northern European populations.[3] Obesity is a major clinical finding, affecting 72%–86% of people with BBS.[3] While ciliary dysfunction may explain several features of BBS, the molecular aetiology of hyperphagia and resulting obesity remains to be fully elucidated. It has been associated with peripheral leptin resistance and abnormal adipogenesis. Type 2 diabetes is prevalent among patients, related to the severity of obesity, and is often found in association with other features of the metabolic syndrome, including hypertension and dyslipidaemia, which if left untreated may reduce life expectancy. In a case–control study comprising 152 patients with BBS who attended two specialist clinics in England compared to 103 individuals matched for age, sex and BMI, the prevalence of the metabolic syndrome in adults with BBS was 54% versus 26% in controls.[4] Among patients with BBS, 76% had obesity, 16% had type 2 diabetes and 15% of the women had polycystic ovary syndrome. Of the 24 patients with BBS who had type 2 diabetes in this study, six patients were diet controlled, eight were taking metformin, and 10 used insulin to manage their diabetes with none reported to have been treated with GLP-1RAs.

The discovery of molecular mechanisms in obesity has progressed with advances in genetic screening,[5] leading to recognition of different clinical presentations depending on the genes involved. Whereas polygenic (common) obesity results from multiple smaller gene mutations having a combined effect on the phenotype, monogenic obesity—a rare and severe form—occurs due to a single gene mutation substantial enough to cause disease. Examples of the latter include mutations in the genes encoding leptin, leptin receptor (LEPR) and melanocortin 4 receptor (MC4R).[5] Pleiotropic obesity syndromes, such as Prader–Willi syndrome and BBS, are associated with mutations in several different genes.

While GLP-1RAs are widely used in the treatment of type 2 diabetes (all agents from this class) and more recently obesity (liraglutide[6] and semaglutide[7]), we are unaware of any reports of their use for weight reduction in BBS in the literature. Pharmacological activation of the widespread distribution of GLP-1 receptors within the CNS, including the hypothalamus, promotes satiety and controls appetite and body weight.[8] Weight regain appears to be common upon cessation of treatment with semaglutide,[9] and long-term weight loss maintenance is likely to require continuous use.

Several novel pharmacotherapies for obesity are on the horizon, including new GLP-1RAs, glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, glucagon analogues, GLP-1/glucagon, GIP/GLP-1 and amylin/calcitonin dual agonists, and GIP/GLP1/glucagon tri-agonists.[10] However, no specific pharmacological treatments exist for hyperphagia and obesity in most rare genetic obesity syndromes. Setmelanotide, an MC4R agonist acting in the brain to regulate food intake and satiety, approved for the treatment of obesity due to LEPR, pro-opiomelanocortin (POMC) or proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiencies in adults and children,[11,12] has been shown to reduce hunger and body weight in individuals with BBS.[13] Further clinical trials are ongoing.

Bariatric surgery, the most effective therapy for severe obesity, is also effective in monogenic obesity due to MC4R deficiency,[14] but is less well studied in pleiotropic obesity syndromes. In people with BBS, sleeve gastrectomy ($n = 5$), Roux-en-Y gastric bypass ($n = 1$), and adjustable gastric banding ($n = 1$) have been reported with

limited, short-term outcome data.[15] Future therapies for BBS could include gene replacement therapy, readthrough therapy, exon skipping therapy and genome editing.[16]

2 | CONCLUSION

We report significant weight reduction with GLP-1RA therapy in a young woman with BBS. Several novel therapeutic agents are on the horizon, but continuous use is likely to be necessary for weight loss maintenance. Futuristic gene therapies may be the holy grail of treatment for BBS and other genetic disorders of obesity.

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ORCID

Smrithi Hema Santhosh https://orcid.org/0000-0003-1060-3158
Akheel A. Syed https://orcid.org/0000-0001-8696-7121

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