Case Report

Severe leptin deficiency in a case of Prader-Willi syndrome: a management challenge

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ABSTRACT

Prader-Willi syndrome (PWS) is a rare multi-systemic genetic disorder with hyperphagic obesity. This complex syndrome is caused by lack of expression of paternally derived genes on chromosome 15q11-13. In classical PWS, major diagnostic features include neonatal hypotonia, feeding problem in infancy, rapid weight gain after infancy, hyperphagia, developmental delay, hypogonadotropic hypogonadism and characteristic facial features. With age, this disorder is further complicated with the development of scoliosis, juvenile diabetes and sleep apnea. Obesity is the most significant health problem for PWS patients. The cause of hyperphagia in PWS is unknown and likely multifactorial. Among the anorexigenic hormones, serum leptin concentration, which signals satiety to the hypothalamus, is found to be appropriately increased in proportion to higher fat mass in patients with PWS. Thus, unusually low plasma leptin levels or relative loss of sensitivity to leptin in PWS subjects could be an important factor in their obesity. We report a young girl with PWS with severe leptin deficiency, morbid obesity and type 2 diabetes mellitus.

Key words: *Prader-Willi syndrome, leptin, obesity.*

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INTRODUCTION

Lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region results in Prader-Willi syndrome (PWS), a complicated multisystem genetic illness. Maternal uniparental disomy 15, paternal 15q11-q13 deletion and imprinting deficiency are the three primary genetic subgroups.[1-5]

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The complex and diverse clinical characteristics of PWS include severe hypotonia in the newborn, feeding issues, childhood-onset hyperphagia, obesity, short height, characteristic facial changes like narrow forehead, hypogonadism, learning disabilities and behavioral issues. Further distinguishing characteristics of this syndrome include scoliosis, hypopigmentation of the skin and hair, juvenile diabetes, delayed healing, small hands and feet and self-inflicted injuries. Sleep apnea resulting from obesity is also a characteristic. Between 1:15000 and 1:50000 is the global incidence. Typically, it affects boys more than girls.[2]

PWS with obesity is a common observation. Although the precise mechanisms underlying the development of obesity are still unknown, they are mostly linked to disruptions in the hypothalamic satiety center and its hormone regulation circuitry, which impact energy expenditure and food intake. It is believed that a number of orexigenic and anorexigenic hormones, including ghrelin, obestatin, pancreatic polypeptide, leptin, adiponectin, resistin play the role.[5] The uncommon genetic condition known as monogenic obesity is

marked by extreme early-onset obesity, aberrant feeding patterns and endocrine abnormalities brought on by mutations in several genes involved in the leptin-melanocortin pathway, which is crucial for the hypothalamic regulation of food intake.[3]

An adipocyte-derived hormone called leptin acts in the brain to control body energy homeostasis.[3] By attaching to and activating a number of distinct leptin receptor isoforms, including the primary signaling isoform, leptin elicits its effects. Agouti-related peptide (AgRP) and neuropeptide Y (NPY) are examples of orexigenic neuropeptides whose expression is downregulated by leptin, whereas anorexigenic neuropeptides like proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) are upregulated. Obesity has been linked to mutations in nearly every step of the route downstream of leptin to melanocortin receptors, including leptin, leptin receptors, POMC, proconvertase-1 and melanocortin receptors 3 and 4.[4]

In contrast to age, sex, and body mass index (BMI)-matched controls, participants with PWS had significantly higher fasting leptin levels. There was no significant association between fasting leptin levels and eating habits. This finding was reported in a study by Goldstone et al.[6] But the majority of research did not identify any difference in leptin levels between individuals with PWS and obesity, since leptin levels were in line with higher adiposity, which is linked to obesity regardless of the cause.[5] Here, a case is going to be presented with PWS along with severe leptin deficiency that combinedly leads to morbid obesity with other related complications.

CASE REPORT

An eight-year-old girl with morbid obesity needed admission through emergency to intensive care unit (ICU) due to breathing difficulties, restlessness, polyuria and new-onset enuresis. Her random blood glucose and glycated haemoglobin (HbA1c) level was 23.2 mmol/L and 13.8% respectively. She was diagnosed with type 2 diabetes mellitus and was discharged with insulin and metformin.

Since the age of three years, the girl has undergone irregular outpatient follow-up in various subspecialties to address her conditions, including obesity, bronchial asthma, grade II adenoid hypertrophy and obstructive sleep apnea. She is the 2nd child of unrelated Bangladeshi parents and was born at term through normal delivery with birth weight 2.8 kg at an Iranian hospital. During her first two weeks of life, she needed admission in newborn ICU due to poor feeding and hypotonia and needed nasogastric feeding to ensure her feeding. She continued to have hypotonia and a feeding issue throughout her infancy. She began to have polyphagia and quickly gained weight after infancy. Her only eldest brother is healthy; both parents are overweight and have diabetes.

She began to exhibit symptoms of morbid obesity at the age of three years, with a BMI of 35.2 kg/m^2 which was > 95th percentile for her age. She had a history of three separate hospital stays between the ages of three and four, during which she was diagnosed with pneumonia, grade II adenoid hypertrophy and morbid obesity. After being released, Bi-PAP was instructed for the night time.

At the age of four years, she was seen in genetic clinic for addressing her severe obesity, polyphagia, slight developmental delay and distinctive phenotypic traits that suggested of having PWS. She has small hands and feet, a depressed nasal bridge, almond-shaped palpebral fissures, epicanthic folds, a broad forehead and thin upper lips (Figure 1. a-e). She additionally had striae, scoliosis and acanthosis nigricans at her neck.

Her fluorescent in situ hybridization (FISH) test result for PWS was negative and her karyotype revealed 46XX. However, the absence of a paternal allele at the 15q11.2-q13.1 region was found in a DNA methylation study**.** No deletion and duplication were detected. Magnetic resonance imaging (MRI) of brain was also normal. Consequently, the clinical diagnosis of PWS resulting from a paternal allele deficiency was confirmed. Her leptin level was 26.9 ng/ml (reference >121 ng/ml), indicating severe deficiency. Thus, it is advised to take a leptin supplement.

Fig.-1a

Fig.-1b

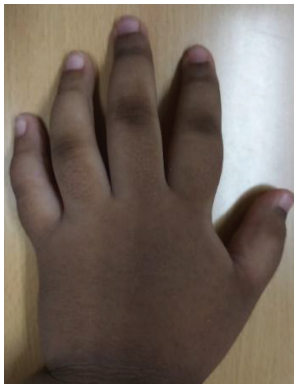

Fig.-1c

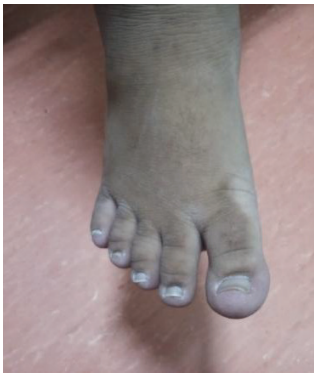

Fig.-1d

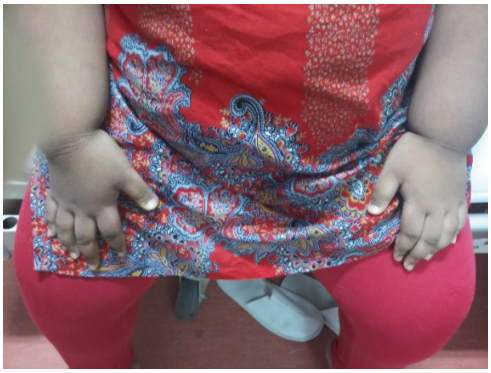

Fig.-1e

Figure 1 (a-e). Girl with characteristic facial features with small hands and foot with obesity

In 2016 at the age of 4 and 1/2 years she underwent adenotonsillectomy and needed Grommet's insertion in ear. At eight and half years age, she also discovered having dyslipidemia and fatty changes in her liver. Her BMI on different occasions is shown in graph (Figure 2).

Now, at her 10 years age, her BMI is 47.3 kg/m^2; she had fair control of her diabetes with metformin, insulin and liraglutide. Routine consultation involving endocrinologist, dietitian and pediatrician as well as continuous motivation for increasing physical activity, regular review of diet charts and dose modification based on capillary blood glucose (CBG) level are being undertaken. The family's support is always valued and encouraged.

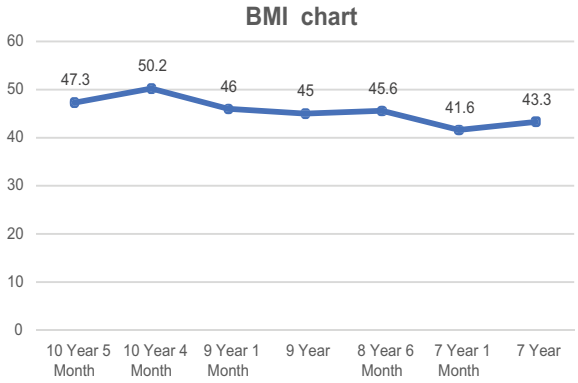

Figure 2. Graphical presentation of BMI of the patient from 7 years to 10 years 5 months

DISCUSSION

PWS is the most widely recognized genetic cause of life-threatening obesity in humans. The main characteristics of this syndrome are severe infantile hypotonia, hyperphagia and early childhood obesity onset, all of which are present in our case. Obesity-related complications in people with PWS include diabetes mellitus, fatty liver, osteoporosis, scoliosis, obstructive sleep apnea, right-sided heart failure, etc.[7] The majority of these conditions are present in the presenting case.

For the purpose of treating PWS patients, it is important to comprehend the pathophysiology of obesity and hyperphagia. While studies have looked into the mechanisms of underlying obesity and hyperphagia in PWS, many questions remain unclear. Hyperphagia and obesity in PWS may result from hypothalamic dysfunction, orexigenic/anorexigenic hormone modulation and energy expenditure.[8] Through appetite dysregulation, a number of orexigenic and anorexigenic hormones are thought to have a role in the development and maintenance of obesity in PWS.[5]

During fasting and hunger, the stomach secretes ghrelin, a powerful orexigenic hormone, is inhibited by meal intake. The majority of investigations but not all of them found that participants with PWS had consistently higher ghrelin levels at any age when compared to age, sex and BMI-matched control children. The intestine releases anorexigenic hormones called pancreatic polypeptide (PP) and peptide YY (PYY) postprandially to promote satiety and prevent overeating. Children with PWS have lower amounts of PP. Adipose tissue secretes the peptide leptin, which is important in controlling hunger and fat storage. The majority of research, however, did not discover a difference in leptin levels between individuals with and without PWS or obesity.[5]

A rare disorder called leptin insufficiency leads to early-onset obesity, mostly through increased appetite and the ensuing overindulgence in food. By suppressing hunger, leptin inhibits energy balance through a variety of hypothalamic responses when it binds to the leptin receptor.[9] In addition to PWS, our patient's low leptin level may be a contributing factor to her morbid obesity.

The most crucial objective of PWS treatment is to manage obesity. Unfortunately, the patient's decreased lean body mass and behavioral issues with controlling their eating make this work challenging. Nutritional counseling and early dietary management are essential for preventing excessive weight gain and the onset of severe obesity.[8]

Recombinant leptin therapy can help people who are leptin deficient. Even in cases of chronic morbid obesity, leptin replacement therapy is beneficial in treating obesity and its side effects, including diabetes mellitus.[3] Children with PWS and leptin insufficiency have better long-term health and developmental results as a result of earlier diagnosis, which has made available treatment more accessible.

Conclusion

Both PWS and leptin insufficiency are linked to morbid obesity, which leads to a number of health problems related to obesity. To give this population the best treatment possible, skilled specialists need to be actively involved. The management of PWS in a multidisciplinary environment is becoming more and more valued. But endocrinologists and general pediatricians should also be aware of leptin insufficiency and the screening and monitoring guidelines for PWS.

Authors' contribution: FZ: Conceptualization, literature search and writing manuscript. NB: literature search and review. NN: literature search and review.

Consent of parents: Taken for publication of case report and images.

Conflicts of interest: Nothing to declare.

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