Bardet-Biedl Syndrome: A Case Study

It is frequently difficult to find an optimal nutritional treatment for children who have rare genetic conditions with multisystem abnormalities because of the complexity of symptoms and the lack of evidence based treatments. Bardet-Biedl Syndrome is an example of one of these conditions. Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive condition that is characterized by polydactyly, rod-cone dystrophy, obesity, and developmental delay (Forsythe & Beales, 2013). Obesity is a significant obstacle for medical professionals when working with these patients. Patients with Bardet-Biedl Syndrome have lower energy expenditure and leptin sensitivity causing them to have rapid weight gain even with caloric restrictions (Rahmouni et al., 2008). Obesity and other clinical manifestations suggestive of Bardet-Biedl Syndrome were observed with one patient at an area hospital, and the registered dietitian was called upon to determine how best to manage her nutrition.

The patient is a 20 month female who was born at 37 weeks gestations weighing four pounds ten ounces. Her mother and father were ages 33 and 37, respectively, Indian, and first cousins. A microarray conducted of the patient's parents showed large segments of homozygosity. The patient's father is a computer engineer and her mother is a registered dietitian. The patient currently lives with her parents, grandparents, and one male sibling, who was diagnosed with familial adenomatous polyposis. The patient's extended family's medical history includes hemochromatosis, gastroesophageal reflux hypothyroidism, hypertension, diabetes, hyperlipidemia, polydactyly, ventricular septal defect, and stroke.

The patient's mother's pregnancy was complicated by hypertension, pre-eclampsia, carpal tunnel syndrome, headache and proteinurea. The patient was in the NICU treated with Cpap for the first two days of life because of work of breathing and temperature instability. The patient was discharged then readmitted two days later for hypothermia. Although the patient was initial fed fortified breast milk via bottle for the first two to three days of life, she transitioned to only breast milk when she began gaining weight too rapidly.

The patient was born with features that suggested possible Bardet-Biedl syndrome. These features included polydactyly, renal echogenicity, and gastrointestinal reflux. She also began to rapidly gain weight several weeks after birth, which is another feature of Bardet-Biedl Syndrome. The patient was not diagnosed with Bardet- Biedl Syndrome three months after birth because she did not exhibit all the necessary criteria; she lacked retinitis pigmentosa. To confirm the syndrome, the patient was enrolled in the NC Genes Research Study which uses whole exome sequencing. NC Gene Research Study found a mutation predicted to be pathogenic in one of the reported genes for Bardet-Biedl Syndrome. Clinical findings were consistent with a diagnosis of BBS10. The BBS10 mutation is associated with earlier occurrence and more severe form of vision problems than other BBS mutations. To test the results from the NC Genes Research Study, the Molecular Genetics Laboratory at University of North Carolina at Chapel Hill Hospital (UNCH) performed Sanger DNA sequencing analysis which showed that the patient was homozygous for a BBS10 variant (BBS10 H395R) which changes histidine to an arginine in the chaperone protein C12ORF58.

Throughout her life, the patient has had a complex medical history. She was diagnosed with a benign heart murmur at the age of five months which was set to be re-evaluated if still present at the age of three years old. The patient also had ongoing constipation which was managed with prunes and

Miralax. As the patient's fluid intake decreased, however, the patient constipation worsened despite the Miralax and treatment is still ongoing for her constipation.

Along with constipation, the patient also saw a gastrointestinal specialist for feeding difficulties. The patient would gag on solids and liquids. The patient had reflux symptoms from one month of age with wet burps and coughing. She underwent two modified barium swallow studies which showed mild-moderate oro-pharyngeal dysphagia with deep laryngeal penetration with thin liquids. A Speech and Language Pathologist recommended slightly thickened liquids and purees to avoid aspiration. The patient was treated with multiple medications including rantidine, omeprazole, and erthyromycin.

At the age of one month of age, a renal ultra sound found echogenic kidneys with possible tubular ectasia. At thirteen months, a MRI of abdomen and pelvis found a conglomeration of lymph nodes anterior to the right kidney with prominent bilateral inguinal, iliac chain, and retroperitoneal lymph nodes. At fifteen months, patient was found to have right SFU (Society of Fetal Ultrasound) grade 2 hydronephrosis, intermittent left SFU grade 1 hydronephrosis, and abnormal increased echogenicity of the medullary pyramids.

The patient's milestones were initially normal. She smiled at thirteen weeks. She rolled from stomach to back and sat up at 6 months. By ten months the patient was pulling herself up and standing for a few minutes. She also began to babble and say three words. After one year of age, however, the patient began to rapidly lose her milestones. She refused to bear weight and could not hold her head up when sitting. She had episodes of loss of tone where her head and body would drop to the right side or she was thrown backwards. The patient also began to experience drop attacks and disconjugated eye movements. Although ataxia is common in Bardet-Biedl Syndrome, motor decline is concerning for Opsoclonus Myoclonus Syndrome. A brain MRI showed hypoplasia of the CNS and atrophy of the corpus callosum with associated hippocampal malrotation. At thirteen months, lab studies showed an increase in B-cells, which could identify an immune system disorder that caused her motor skills regression. The patient was treated with IV immunoglobulin G (IVIG) and steroids in order to suppress her immune system to see if her symptoms improved. The symptoms including head movements and eye movements improved after IVIG infusion and high dose dexamethasone, but the patient still refused to bear weight on her feet and would fall back when sitting up. The patient was diagnosed with Opsoclonus Myoclonus Syndrome (OMS). The patient's symptoms returned several weeks after treatment and she was given Rituximab infusion. She initially showed improvements with treatment but after several weeks her symptoms returned. She was given two more Rituximab infusions and Ofatumumab. Rituximab and Ofatumumab are anti CD20 IgG1k human monoclonal antibodies that were given in attempt to suppress her immune system and improve her symptoms. At 19 months of age the patient began to have insomnia and rage attacks which are common in OMS. The patient would wake up angry and would not calm down unless given formula. The patient was prescribed trazadone, melatonin, and clonidine to improve sleep and behavior. The patient was also referred to a multiple disciplinary teams at an outside hospital for management of symptoms.

Patient had an Electroretinography at fifteen months of age which showed abnormalities consistent with retinitis pigmentosa. The patient was prescribed glasses for myopia. Her ophthalmologist did not believe that her disconjugated eye movements were related to ocular/retinal/myopia issues.

Throughout her life, the patient's mom reported that the patient had chronic colds with noisy breathing while eating and sleeping. She also had stertor and intermittent stridor. The patient was hospitalized multiple times for wheezing, fevers, and respiratory infections. She had two bronchoscopy

procedures. The bronchoscopy performed at 10 months found moderate tracheomalacia with apparent outpouching in posterior membrane of trachea, mild adenoidal hypertrophy, a bifid uvula, and bronchitis. The second bronchoscopy showed various levels of upper airway narrowing but little adenoidal tissue. She was treated with Pulmicort for reactive airway disease and Flonase to reduce adenoid size and improve airway patency. Her increased vomiting also negatively impacted her pulmonary function. The pulmonary team is still trying to find an effective treatment plan for her.

The patient was initially followed by a dietitian to evaluate growth and oral intake. During the first months of life, she began gaining weight rapidly. Her weight gain velocity was twice as rapid as children her age without Bardet-Biedl Syndrome. She also had reflux symptoms including wet burps and vomiting. She was seen by the area hospital dietitian at seventeen months. Her intake at that time consisted of 16-20 ounces of Enfagrow Gentlease, a partially hydrolyzed infant formula that is easier for infants to digest than standard formula. She also ate three meals per day that were diverse and meticulously portioned by her mother who is a registered dietitian. The patient was eating 600-900 kcal/day which is 52 kcal/kg. 52 kcal per kg is significantly lower than the DRI for her age which is 82 kcal/kg (Bunting et al., 2013).

Patient was experiencing reflux symptoms and constipation which were being addressed by Gastroenterology. Her formula was changed to Nutramigen Toddler, a hydrolyzed formula and then to Neocate Infant, an elemental formula and the volume of formula was decreased in attempt to address her GI symptoms and reduce her weight gain. The dietitian also recommended an increase in daily fluids to help constipation and ensure adequate fluid intake. Despite these changes to her formula, the patient continued to gain weight rapidly. Since the patient was also constipated and vomited whenever she drank water her formula recipe was changed to reduce calories and 8 ounces of water was mixed into her pureed foods to add fluids.

During my visit, I observed the patient and worked with her mother to create a nutrition plan that would best suit the patient's needs. At first glance, the patient looked older than 20 months. She was larger in size and taller than most children her age. She was unable to hold her weight up when she sat and her mother had to hold her head. The mother had difficulty holding her due to her size and struggled when the patient's diaper needed to be changed.

The mother had met with the pediatric registered dietitian several times before this visit and told me the various changes that they had made. The mother was very frustrated at the fact that despite the changes in formula type, volume, and recipe, the patient continued to gain weight quickly and her GI symptoms had not improved. The patient was also still vomiting when drinking water. Due to her emesis and reduced formula volume, there was a concern for inadequate fluid intake and dehydration. The RD had recommended adding an additional eight ounces of water mixed into her pureed foods each meal. A daily liquid multivitamin was also indicated because it was unclear the amount of nutrients from formula and foods she was able to absorb due to her emesis and the reduction in formula. While her formula recipe and volume were not changed at this visit, the mom and RD discussed working with a RD that specializes in Bardet-Biedl syndrome and possibly trying a Ketogenic or modified Atkins diet to reduce weight gain.

The patient discussed was diagnosed with Bardet-Biedl Syndrome. Bardet Biedl Syndrome (BBS) is a rare pleiotropic genetic disorder characterized by clinical features such as polydactyly and retinal pigmentosa (Forsythe & Beales, 2013). Although genetic testing can be performed early in life, the Bardet-Biedl Syndrome phenotype can change over time. Most individuals who are suspected to have BBS are diagnosed during adolescence or early adulthood. Some clinical features can be observed at

birth such as polydactyly; others such as rod-cone dystrophy usually arise within the first ten years of life. Other clinical features of Bardet-Biedl Syndrome include obesity, genital and renal anomalies, learning difficulties, and developmental delay (Forsythe & Beales, 2013). To be diagnosed with Bardet-Biedl Syndrome, the patient must exhibit four of the primary features of BBS or three primary features and two secondary features (Forsythe & Beales, 2013). The primary and secondary features of Bardet-Biedl Syndrome are found in Table 1.

Gene sequencing can be used to confirm the diagnosis of Bardet-Biedl and has 80% success. The prevalence of Bardet-Biedl syndrome differs among different locations. The prevalence of BBS is 1:160,000 in Northern European countries (Forsythe & Beales, 2013). Higher prevalence has been found in areas such as Kuwait and Newfoundland. The prevalence of Bardet-Biedl syndrome in Kuwait is 1:13,500 (Forsythe & Beales, 2013) and 1:18,000 (Fan et al., 2004). A possible reason for the increased prevalence in these areas is the increased amount of consanguinity that exists (Forsythe & Beales, 2013).

Bardet-Biedl Syndrome is typically inherited in an autosomal recessive pattern but a few individuals have inherited the syndrome in a triallelic manner (Fan et al., 2004). Sixteen Bardet-Biedl genes have been identified (Forsythe & Beales, 2013). Although there are regional difference of prevalence of mutations, the most common mutations are BBS1 (23%) and BBS10 (20%) (Forsythe and Beales, 2013). BBS1 mutations have been linked to a specific region in Newfoundland. The mutation has been identified as a missense mutation in which T was replaced with a G in exon 12. This mutation results in a homozygous state and causes expression of a different amino acid (M390R) (Fan et al., 2004). BBS1 mutation and other mutations common to BBS have been shown to affect cilia function and maintenance, leptin receptors, and POMC neurons.

Table 1 Diagnostic features and prevalence in BBS

Features	Frequency
Primary features	
Rod-cone dystrophy	93%
Polydactyly	63–81% All four limbs: 21% Upper limbs only: 9% Lower limbs only:21%
Obesity	72–92%
Genital anomalies	59–98%
Renal anomalies	53%
Learning difficulties	61%
Secondary features	
Speech delay	54–81%
Developmental delay	50–91%
Diabetes mellitus	6–48%
Dental anomalies	51%
Congenital heart disease	7%
Brachydactyly/ syndactyly	46–100%/8–95%
Ataxia/ poor coordination	40–86%
Anosmia/hyposmia	60%

(Forsythe and Beales, 2013)

Bardet-Biedl Syndrome is a rare disease with ongoing research being conducted in order to gain more information about the nature of the disease and the most optimal treatment procedures for patients. Obesity is a huge concern for BBS patient such as the patient described above. One reason for obesity is as result of the Bardet Biedl Syndrome the patient may have decreased energy expenditure. While the DRI for her age is appropriate for sedentary children, the patient may have an even lower energy expenditure than sedentary children. The mother reported the patient had low activity level, she would crawl infrequently and spent most time lying down. The patient slept four to five hours per night due to insomnia. In a study with BBS knockout mice, Rahmouni et al. (2008) found that given the same amount of food for 13 weeks, BBS mice had 2-3 times higher fat deposits then wild type mice. The study suggests "these results indicated that BBS mice have low energy expenditure, which may contribute to obesity in these animals" (Rahmouni et al., 2008).

Another component of Bardet-Biedl Syndrome is the effect on cilia and satiety signaling. Cilia are organelles located on exterior of cells that are responsible for cellular motility and signaling. In Bardet-Biedl Syndrome, normal cilia function is disrupted which can cause kidney disease, retinal degeneration, and obesity (Gupta, Prodromou, & Chapple, 2009). "One emerging and important mechanism to achieve weight control in mammals is the involvement of primary cilia, which presumably transduce satiety signals via appetite-modulating receptors, such as the leptin receptor, Sstr3, and Mchr1 as well as other signaling molecules including AC3 (Heydet et al., 2012). The loss of CNS cilia, especially POMC expressing neurons of the hypothalamus which are involved in energy homeostasis, results in hyperphagia. This hyperphagia causes the animals to become obese and develop metabolic syndrome complications. Hypothalamic cilia have been shown to be associated with the management of satiety (Heydet et al., 2012).

The cilia dysfunction is suggested to be affecting leptin receptor signaling (Gupta, Prodromou, & Chapple, 2009). One study of BBS knockout mice showed that despite similar treatment, BBS knockout mice had increased levels of plasma leptin and higher level of leptin resistance than wild type mice. Leptin is a peptide hormone secreted by the adipose tissue that is responsible in modulating energy homeostasis. If an individual has leptin resistance, they do not have satiety cues and will consume more food than they need.

The Bardet-Biedl Syndrome patient exhibits the hyperphagia that is common to Bardet-Biedl Syndrome. At home, the mother reported that the patient constantly wanted to eat and would be become angry when she was denied food. The patient would wake up during the night screaming for food and would not go back to sleep unless she was fed. The mother tried to give the patient water during the night to calm her down but it would not satisfy her and she would continue to cry. In attempt to decrease the calories that the patient was ingesting, the mother would give the patient watered down formula at night. The mother was also cutting the patient's food in very small pieces so that the meal will last longer. Throughout the visit the patient was extremely fussy, using sign language to sign "more" to indicate that she wanted more food. When she was not given more food she began to scream and violently move her extremities. When her mother gave her a bottle of formula, she drank it at a rapid speed and then signed "more" again. After the feeding, the patient showed signs of reflux with wet burps and small amounts of spit up. The mother discussed her frustrated at her daughters eating habits. While the mother tries to portion the patient's meals, she also feels guilty and upset when she cries that she is hungry. The patient becomes angrier if she is not fed and will scream uncontrollably.

Currently, there are no official nutrition DRIs for Bardet-Biedl syndrome. The lack of appropriate DRIs for this syndrome makes it difficult for nutrition professionals to provide accurate nutrition recommendations. Recently, the mother went to a Bardet-Biedl Syndrome conference and will be

working with a registered dietitian that specializes in Bardet-Biedl Syndrome. A BBS specialist will be able to provide more appropriate nutrition recommendations for patients with Bardet-Biedl Syndrome as well as address the emotional stress of hyperphagia. Hopefully as more information emerges on BBS and effective treatment methods, more registered dietitians will be trained to treat Bardet-Biedl Syndrome patients

Bardet-Biedl Syndrome is a rare autosomal recessive genetic disorder that presents with multiple physical findings, including polydactyly and obesity. The patient observed was diagnosed with Bardet-Biedl Syndrome and exhibited many of the clinical features that are consistent with the syndrome. Since BBS is rare, studies are still ongoing to discover the mechanism of the disease and identify the best treatment options for patients with Bardet-Biedl Syndrome. Future research is indicated to provide nutrition professionals the information needed to effectively treat the various problems associated with Bardet-Biedl Syndrome, especially hyperphagia.

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