



**Patient-Led Listening Session on Hypothalamic Obesity
October 22, 2021**

Objective of Session

Hypothalamic obesity (HO) is a condition that develops from injury to the hypothalamus often due to a brain tumor, typically craniopharyngioma, or treatment of that tumor. The objective of this listening session was to facilitate an understanding of the impact of HO on patients, caregivers and families of the patient and to differentiate this form of obesity from standard obesity. The Raymond A. Wood Foundation hopes that by sharing information regarding the medical, psychological and social implications of this disease with the FDA, we can make progress towards a standard of care and treatment for this challenging condition.

Summary of Topics Discussed

Overview of HO

Hypothalamic obesity (HO) is typically caused by a brain tumor in the hypothalamic-pituitary axis of the brain. These tumors, namely craniopharyngioma, are diagnosed in both children and adults and can result in multiple endocrine disorders that severely impact quality of life.

Dr. Harvey Cushing, the father of modern neurosurgery, declared craniopharyngiomas “the most formidable of intracranial tumors.”

Hermann Mueller, a craniopharyngioma researcher elaborates in a report entitled *Hypothalamic-Pituitary Outcome after Treatment for Childhood Craniopharyngioma*, “Disease- or treatment-related hypothalamic damage leads to disturbed hunger-satiety and thirst feelings, decreased energy expenditure, behavioral problems, disturbances of

circadian rhythm, temperature dysregulation, and pituitary dysfunction. These children are at great risk for developing metabolic syndrome and comorbidities leading to premature mortality.”

Hypothalamic Obesity is a spectrum disorder that can present in continuous weight gain despite caloric restriction and exercise and may also present with hyperphagia, the inability for the person to reach satiety and experiences unrelenting hunger.

Presenters in the Patient Listening Session on Hypothalamic Obesity included a clinician and HO researcher, a survivor diagnosed with a craniopharyngioma as a child and grew up with HO, a parent-caregiver and teenager with HO and hyperphagia, a registered dietician and nutritionist who is also a parent of a child with HO, a survivor diagnosed as an adult with craniopharyngioma who developed HO and hyperphagia and a parent-caregiver of a young adult with HO and hyperphagia.

Topics included diagnosis and lack of treatment, quality of life challenges, social and behavioral issues including stealing and hoarding food, caregiver burden, implications on family, HO versus standard obesity and the limited effect of lifestyle modifications in diet and exercise, and the desperate need for a treatment.

Diagnosis

It was indicated that HO is characterized by rapid weight gain after treatment of brain tumor or other injury to the hypothalamus. Diagnosis takes into consideration at least one endocrinopathy which is additional evidence of hypothalamic damage. Patients can present with abnormal eating behavior, low energy expenditure, hyperinsulinemia and disrupted circadian function. Further complications of HO include diabetes type II, fatty liver, and other chronic health issues.



Current State of Treatment

According to presenting clinician and researcher, HO is more treatment-recalcitrant than standard obesity. A treatment example of GLP1RA, used to treat common obesity, had a variable response rate in HO compared to common obesity and required more individualized treatment. There are also access challenges with this medication particularly with insurance coverage.

There is no standard of care or treatment for hypothalamic obesity. Practitioners are not familiar with HO leading families to fend for themselves finding their own path to care.

Currently there is no FDA approved treatment for hypothalamic obesity.

Quality of Life (QoL)

A graph was shared showing how QoL is negatively impacted in multiple domains including self-esteem, cognition, body image, social and emotional functioning, and physical functioning. Extent of the effect on QoL is related to the extent of the tumor.

The presenters shared insights on day to day living with this condition including shame brought on by stealing and hoarding food, locking up and policing food, social isolation and inability to attend holiday and family functions or other social occasions, inability to keep jobs because of food theft, the feeling of never being satisfied after eating, the impact on family life and siblings and the frustrations of not having treatment options.

Living with HO - Survivors' Perspectives

A teenage survivor shared his experience of living with HO and the constant hunger and focus on where or how he would get the next meal/snack. He felt shame for lying and stealing and felt that among all of the complications from the tumor including low vision, adrenal insufficiency and diabetes insipidus, HO was the most difficult. He tried shots and pills but his condition worsened. He did not have friends and his family did not trust him to be on his own. He had considered suicide.



A young adult survivor was diagnosed with a craniopharyngioma as a child and immediately experienced weight gain after treatment. She also experienced gastroparesis which caused severe stomach pain. She shared that she had a sense of being judged by friends for her food choices and weight gain as well as judgement from doctors who did not understand the condition. She was comparing herself to her sister who was normal weight while eating the same foods. After trying a very extreme, low calorie/low carb diet, she was able to lose weight but the weight loss is not sustainable long-term. She participated in a clinical trial of oxytocin for HO but it did not experience any results in weight reduction.

An adult exercise enthusiast was diagnosed and treated for a craniopharyngioma and immediately put on weight and developed hyperphagia after surgery. Her thoughts are hyper-focused on food and, despite exercising an hour a day six days a week and restricting calories to 1500 a day, she still battles weight. She felt that she would have rather had the tumor take her than to face the complications of HO.

The Impact of Diet and Exercise on HO

A registered dietician and mother to a survivor with HO shared that this condition has more in common with starvation than standard obesity. People suffering from starvation or HO will eat out of the trash, have a constant hunger signal, will steal food and have a low metabolism. HO occurs in a spectrum of mild, and severe and The difference between a person in starvation and a person with HO is high insulin levels and weight gain/fat storage.

HO presents in a spectrum of mild, moderate to severe. Mild cases may respond to a strict low carbohydrate diet with exercise but will likely never reach or maintain a healthy weight, severe cases may slow weight gain with strict diet and exercise but cannot typically lose weight.

With HO, unlike standard obesity, insulin levels do not drop to basal levels between meals or in response to changes in diet and weight loss. Lipolysis (fat breakdown) is thought to be limited by the high insulin to glucagon ratio and the resulting anabolic state that the



damaged hypothalamus perpetuates. Disturbances of circadian rhythm and excessive daytime sleepiness due to hypothalamic damage, lack of energy from insufficient hormone replacement and lower baseline metabolism all contribute to the challenges of managing this condition.

Medications for HO

In desperation for a solution, one caregiver went on a quest to research and experiment with the combination of oxytocin and naltrexone to deter hedonic food seeking. The results were successfully measured by decreased food seeking, lessening of anxiety around food and allowed the family to unlock the cabinets and refrigerator. Food intake still needs to be monitored as rapid weight gain is still a challenge.

Another caregiver reported multiple medications used for treatment of standard obesity with no success in her young adult son living with hyperphagia and HO. The patient also underwent gastric sleeve surgery which is sometimes recommended for extreme cases but had no success in weight loss or reduction of hyperphagia.

Caregiver Burden/ Impact on Family

A caregiver reported that her son was brought home by police at age 10 after sneaking out of the house in the middle of the night to get candy at a nearby store. He is now in his 20's and she reports that they have tried everything to help with his extreme anxiety around food and feels like she is failing her son. HO is described as a "living hell" because the person can not go unsupervised, it creates toxic family dynamics, puts a strain on marriages and sibling relationships, creates isolation and there is little support available to caregivers or survivors.

Conclusion

Hypothalamic obesity is a rare and complex disorder characterized by hyperphagia and excessive weight gain caused by treatments of hypothalamic brain tumors or injury to the



hypothalamus. Today's patient listening session shared the perspectives on the challenges of living with and managing this condition and the need for more research and treatments that address the range of issues.

FDA Offices Represented

Office of the Commissioner (OC) – 5 offices

- OC/OCPP/OPA- Office of Clinical Policy and Programs/Office of Patient Affairs (*organizer*)
- OC/OCPP – Office of Clinical Policy and Programs
- OC/OCPP/OCliP – Office of Clinical Policy and Programs/Office of Clinical Policy
- OC/OCPP/OCP – Office of Clinical Policy and Programs/Office of Combination Products
- OC/OCPP/OOPD - Office of Clinical Policy and Programs/Office of Orphan Products Development

Center for Biologics Evaluation & Research (CBER) – 2 offices

- CBER/OCD - Office of the Center Director
- CBER/OTAT/DCEPT/GMBII – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharm/Tox/General Medicine Branch II

Center for Devices and Radiological Health – 3 offices

- CDRH/OPEQ/OHTIII – Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIA - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III A
- CDRH/OPEQ/ORP/DRPI – Office of Product Evaluation and Quality/Office of Regulatory Programs/Division of Regulatory Programs I

Center for Drug Evaluation and Research (CDER) – 4 offices/divisions



- CDER/OND/OCHEN/DDLO – Office of New Drugs/Office of Cardiology, Hematology, Endocrinology and Nephrology/Division of Diabetes, Lipid Disorders and Obesity
- CDER/OND/ODES/DCOA – Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBII – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics II

Patients Represented

Patient 1

Female in her 20's diagnosed with a craniopharyngioma as a child and developed HO

Patient 2

Teenage male, diagnosed with a craniopharyngioma as a child and has HO and hyperphagia

Patient 3

Female in her 40's diagnosed with craniopharyngioma as an adult and developed HO and hyperphagia

Caregiver 1

Mother to teenage male, , diagnosed with a craniopharyngioma as a child and has HO and hyperphagia

Caregiver 2

Mother to a teenage male, diagnosed with a craniopharyngioma as a child and has HO and hyperphagia



Caregiver 3

Mother to a male in his 20's, diagnosed with a craniopharyngioma as a child and has HO and hyperphagia

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects Raymond A. Wood Foundation's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of hypothalamic obesity, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire [disease or condition] patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

