ENDO TOPICAL CATEGORY

ADIPOSE TISSUE, APPETITE, AND OBESITY

Experiences and Observations With Acquired Hypothalamic Obesity: A Qualitative Interview Substudy

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Background

- Acquired hypothalamic obesity (aHO), caused by injury to the hypothalamus, is commonly characterized by insatiable hunger and abnormal food-seeking behaviors (hyperphagia) that result in accelerated weight gain and reduced health-related quality of life.[1]
- There are no treatments specifically approved for aHO.[2]
- Setmelanotide is being investigated as a treatment for aHO in a phase 3, randomized, double-blind, placebo-controlled trial (TRANSCEND; NCT05774756).[3]
- To support the evaluation of treatment benefit potentially associated with setmelanotide in this context of use, it is necessary to understand patients' and their caregivers' lived experiences with aHO.

Objective

- To characterize the burden of aHO post–hypothalamic injury, before initiating treatment in TRANSCEND and after, to support the assessment of key aHO treatment outcomes based on the perspectives of trial participants and caregivers.

Methods

- In-depth, 75-minute qualitative interviews were conducted remotely from July 2024 to January 2025 with eligible English-speaking individuals in the United States. These individuals included TRANSCEND trial participants who were aged ≥ 12 years and able to self-report; for trial participants aged < 12 years or ≥ 12 years and unable to self-report, their primary, full-time, adult caregivers were interviewed instead.
- Interviews, which were completed within a 14-day window after a trial participant's end-of-treatment visit, followed a semistructured interview guide tailored to facilitate discussion about trial participants' experiences or caregivers' observations regarding changes in weight, hunger, and energy levels.
  - Those interviewed were also asked to describe any changes in these concepts while participating in the TRANSCEND trial and the meaningfulness of any changes experienced.
- Qualitative interview data analysis and reporting was completed prior to unblinding.
- Interviews were audio recorded and transcribed for thematic analysis using ATLAS.ti (https://atlasti.com/).

Results

Characteristics of Those Interviewed

- 30 individuals (4 adolescent trial participants, 10 adult trial participants, and 16 caregivers) consented and were interviewed (Table 1).

Table 1. Key Characteristics of Those Interviewed

Characteristic	Adolescent trial participants aged ≥ 12 years to < 18 years (n = 4)	Adult trial participants aged ≥ 18 years (n = 10)	Caregivers of trial participants[a]	
			Aged < 12 years (n = 8)	Aged ≥ 12 years (n = 8)
Patient age in years, mean (SD)	15.0 (1.6)	28.2 (8.7)	7.3 (2.1)	19.5 (4.3)
Patient sex, n[b]	3 F, 1 M	6 F, 4 M	5 F, 3 M	7 F, 1 M
Patient age in years at time of injury, mean (SD)[c]	7.5 (2.6)	12.5 (7.6)	5.0 (2.4)	6.6 (2.2)

F = female; M = male; SD = standard deviation.
[a] Of the 16 caregivers of trial participants, most were mothers (15/16); 1 was the father of a trial participant aged ≥ 12 years.
[b] As assigned at birth.
[c] Ages were self-reported. One adult trial participant reported that she experienced injury to the hypothalamus resulting from the growth of a tumor (unrelated to surgery or injury); as such, she could not provide a specific date for the injury and instead provided the date she was diagnosed with aHO. The age at diagnosis was used for the summary statistics.

Impacts of Hypothalamic Injury Before Treatment Initiation in the TRANSCEND Trial

- All 30 of those interviewed reported experiencing or observing weight gain, which was described as rapid and extreme, with several caregivers reporting that their young child's body weight doubled or tripled post–hypothalamic injury.
  - Most individuals (n = 18) reported prior prescription medication use to manage weight; stimulants (n = 9) and glucagon-like peptide-1 receptor analogs (GLP-1RAs) (n = 7) were most used. Only 5 individuals reported weight loss with these medications, which was described as limited or temporary.
- All those interviewed reported increased hunger post–hypothalamic injury, with 29 indicating that they or their child never or rarely felt full (Table 2).
  - Individuals described intense, unrelenting hunger that led to increased food consumption and a lack of control when eating (n = 28). This lack of control and associated food-seeking behaviors were the most bothersome aspects of aHO, as reported by caregivers. Both trial participants and caregivers reported a constant struggle between the trial participants' food-seeking behaviors and the caregivers' attempts to monitor and limit food.
- Additional factors reported as contributing to weight gain post–hypothalamic injury included decreased energy levels (n = 29) and reduced physical activity (n = 28).
- Symptoms and impacts of aHO were described as contributing to social, familial, and mental/emotional burden.

Representative Quotes for Post–Hypothalamic Injury Impacts

Weight gain

"I gained so much weight. It's been, sorry, it's been traumatizing for me. It was so scary. My weight went up almost 300 pounds and it's been really hard." (Adolescent)

"It went up a lot...The weight drastically was added on, basically as soon as I got out of surgery." (Adult)

"But the weight just came on and it came on drastically...He went from 37 pounds to 130 pounds in just a little over a year." (Caregiver)

Change in eating habits

"It was almost like I had a black hole in my stomach." (Adult)

"...he would put anything in his mouth, Play-Doh, he'd go through the trash, he would go try to go through the fridge, he'd try to get into everything, it was just constant battle." (Caregiver)

"It was mostly about I had basically zero control whatsoever...it was hard to tell no to myself." (Adolescent)

Increased hunger/hyperphagia frequency and intensity

"Oh, it was constant. It was nonstop. She was waking up in the middle of the night in her sleep crying out for food and saying she was hungry." (Caregiver)

"Tremendously changed. I was always hungry. My mom had to put a lock on the kitchen…Food was my life. Food was everything." (Adolescent)

"I was very focused, very concentrated on I need food and I need it right now, and nothing else really mattered. At that point when I was stealing and buying, stealing, hiding food because of this constant, oh my God, if I don't have food, I'm going to die, in a sense." (Adult)

Decreased energy levels and physical activity

"Like walking up and down the stairs was always a problem. Going to a store and walking around...I remember always looking around, looking for somewhere to sit..." (Adolescent)

"My energy level was super high before my surgery. I played tennis a lot and my mom always called me an Energizer bunny. And after surgery, it dropped completely. I had no energy at all." (Adult)

"She hardly had energy to do anything...She might try to do something with other kids and she couldn't keep up." (Caregiver)

Mental/emotional, social, and familial impacts

"It was just kind of a...felt like a disappointment, kind of, that I couldn't do what I used to be able to do normally." (Adult)

"I felt like a mix of embarrassed, bad about myself, for sure. All the sweets I've been sneaking." (Adolescent)

"Just the way it controlled her life. She was very, very heartbreaking to watch...She wouldn't enjoy things. It was always in the back of her mind." (Caregiver)

Table 2. Clinical Consequences Post–Hypothalamic Injury

Impact	Adolescent trial participants aged ≥ 12 years to < 18 years (n = 4)	Adult trial participants aged ≥ 18 years (n = 10)	Caregivers of trial participants		Total (N = 30)
			Aged < 12 years (n = 8)	Aged ≥ 12 years (n = 8)	
Weight gain	4	10	8	8	30
Increased hunger frequency	4	10	8	8	30
Increased hunger intensity	3	9	8	8	28
Changes in eating habits					
Never felt full	2	3	6	4	15
Less likely to feel full	2	7	2	3	14
Decreased control of eating	3	9	8	8	28
Increased amount of food eaten	3	9	8	8	28
Decreased energy levels	4	9	8	8	29
Fatigue[a]	4	9	—	—	
Decreased physical activity	4	8	8	8	28

[a] The concept of fatigue was probed only with patient participants and not with caregivers.

Treatment Aspirations Before Treatment Initiation in the TRANSCEND Trial

Among the reasons for participating in the trial, individuals most commonly described hoping to:

- **Lose weight** (n = 19)
- **Reduce hunger/hyperphagia** (n = 13)
- **Increase energy** (n = 9)
- **Improve bloodwork or overall health** (n = 8)

"Well, I was hoping to get down to a normal [body mass index]." (Adult)

"For me, it was kind of like this might be my last hope to lose the weight and get healthy again." (Adult)

Key Improvements During the TRANSCEND Trial*

***Qualitative interview data analysis and reporting were completed prior to unblinding.**

Weight loss was reported by 23 of the 30 interviewees (12 patients and 11 caregivers) while participating in TRANSCEND. The key factors driving weight loss (as reported by those interviewed) were:

- **Decreased hunger and increased satiety**
- **Greater control of eating**
- **Increases in physical activity**
- **Increases in energy**

These outcomes were described as being ultimately very meaningful.

"…just significant... less hunger" (Adult)

"It literally brings tears to our eyes, so [it is] pretty meaningful." (Caregiver)

"It's like huge, beyond. I remember being so miserable and just horrible about myself...now I feel good." (Adolescent)

"It's meaningful to me because I feel like I'm in control of myself...I feel like a normal person who just wants to have normal meals and move on and not have it consume my life." (Adult)

"I think him not feeling starving all of the time has significantly impacted his ability to participate in the world...to see him find joy in other things has been a really big impact." (Caregiver)

Conclusions

- This study's findings provide a better understanding of the burden of aHO from the perspective of trial participants and caregivers.
- Experiences with aHO post–hypothalamic injury were characterized by substantial hunger, lack of control of eating, poor satiety, reductions in activity/function, and weight gain, which had severe impacts on trial participants' and caregivers' overall quality of life.
- During the TRANSCEND trial, improvements in weight loss, hunger, satiety, control of eating, physical activity, and energy levels were reported by participants and caregivers, who often described these changes as meaningful and contributing to improved quality of life.
- These qualitative interview results support the assessment of these core concepts (change in weight, fatigue, and physical activity/function) in aHO clinical trials.

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