A US Real-world Study of Weight Trajectory and Causes of Hypothalamic Damage Among Patients With Acquired Hypothalamic Obesity

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Introduction

- Acquired hypothalamic obesity (aHO) is a disease characterized by accelerated and sustained weight gain caused by an injury to the hypothalamus for which no approved therapies currently exist[1,2]
- Hypothalamic injury can occur because of the presence of a tumor and/or its associated treatment. Other forms of injury due to traumatic brain injury, inflammation, or stroke are less often reported in the literature but may still be common underlying pathologies of aHO
- Evidence around real-world patient characterization, aHO cause, treatment journey, and disease burden is limited. A recent German study is one of the first to adopt a claims-based algorithm to identify patients with aHO to better understand epidemiology estimates and healthcare resource use[3,4]; however, relevant evidence in the United States is lacking
- This study evaluated the real-world patient demographic and clinical characteristics as well as weight gain trajectory by causes of hypothalamic injury in adult patients with aHO in the United States

Methods

- A retrospective observational study was conducted using the TriNetX claims/electronic medical records linked database from 2010 to 2023
- Adult patients were selected on the basis of the following criteria (first such event defined as index hypothalamic insult):
  - Clinical evidence of hypothalamic insult as indicated by the International Classification of Diseases, Tenth Revision (ICD-10) codes or Current Procedural Terminology (CPT) codes (defined as relevant brain tumor followed by surgery and/or radiation treatment, or relevant brain-related trauma event) that potentially led to hypothalamic damage
  - Evidence of accelerated weight gain, defined as ≥5% body mass index (BMI) increase and ≥1 additional aHO indicator (panhypopituitarism, diabetes insipidus [also known as arginine vasopressin deficiency (AVP-D)], hyperphagia, hypothalamic dysfunction, or desmopressin use), or ≥15% BMI increase without any aHO indicator, during 12-month period following hypothalamic insult (defined as follow-up period)
  - Two sets of sensitivity analyses were conducted around the definition of accelerated weight gain when indicators were not present; that is, ≥5 BMI point increase or ≥20% BMI increase during the follow-up period. In both cases, ≥5% BMI increase and ≥1 additional aHO indicator would still qualify as accelerated weight gain
  - No evidence of rapid weight loss (≥5% BMI decrease) before hypothalamic insult nor other potential significant weight gain 2 years before hypothalamic insult and during follow-up
- Descriptive analysis was conducted; mean, median, and standard deviation (SD) were reported for continuous measures and the number (percent) for categorical measures

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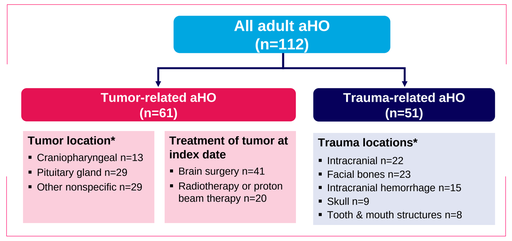
References: 1. Rose et al. *Obesity (Silver Spring)*. 2018;26:1727-1732. **2.** Roth et al. *Obesity (Silver Spring)*. 2015;23:1226-1333. **3.** Witte et al. *J Neuroendocrinol*. 2024;36:e13439. **4.** Müller et al. *Sci Rep*. 2025;15:2118.

Results

Study Population and Index Hypothalamic Insult

- As shown in Figure 1, 112 patients were selected, with 61 tumor-related and 51 trauma-related cases
  - Among them, 17 (15.2%), 26 (23.2%), 6 (5.4%), and 19 (17.7%) had clinical evidence as indicated by ICD-10 or CPT codes of diabetes insipidus (AVP-D), hypopituitarism, hypothalamic dysfunction, and use of desmopressin, respectively, also known as aHO indicators
- Sensitivity analyses were conducted around accelerated weight gain definition without additional aHO indicators; 94 patients (49 tumor related and 45 trauma related) were identified when ≥5 BMI point increase was required, and 76 patients (43 tumor related and 33 trauma related) were identified when ≥20% BMI increase was required

Figure 1. Summary of Index Hypothalamic Insult Events



*Not mutually exclusive. aHO, acquired hypothalamic obesity.

Table. Patient Baseline Characteristics

		By baseline BMI class					By index insult type		
	All adults (n=112)	Under/Normal weight* (n=35)	Overweight† (n=40)	Obesity class I‡ (n=17)	Obesity class II§ (n=13)	Obesity class III¶ (n=7)	Trauma-related (n=51)	Tumor radiation related (n=20)	Tumor surgery related (n=41)
Age, mean (SD), y	48.5 (13.5)	45.3 (15.6)	50.2 (11.3)	51.1 (13.8)	46.7 (15.0)	51.9 (8.8)	43.8 (13.8)	53.8 (14.4)	51.7 (10.9)
Female, n (%)	59 (52.7)	20 (57.1)	18 (45.0)	8 (47.1)	6 (46.2)	7 (100.0)	23 (45.1)	14 (70.0)	22 (53.7)
Race, n (%)									
White	71 (63.4)	19 (54.3)	27 (67.5)	14 (82.4)	7 (53.8)	4 (57.1)	31 (60.8)	15 (75.0)	25 (61.0)
Black or African American	35 (31.3)	13 (37.1)	11 (27.5)	3 (17.6)	6 (46.2)	2 (28.6)	19 (37.3)	4 (20.0)	12 (29.3)
Asian	3 (2.7)	1 (2.9)	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (5.0)	1 (2.4)
Other/Unknown	3 (2.7)	2 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	3 (7.3)
Insurance type, n (%)									
Commercial	37 (33.0)	7 (20.0)	17 (42.5)	4 (23.5)	6 (46.2)	3 (42.9)	13 (25.5)	9 (45.0)	15 (36.6)
Medicaid	36 (32.1)	16 (45.7)	10 (25.0)	3 (17.6)	3 (23.1)	4 (57.1)	21 (41.2)	5 (25.0)	10 (24.4)
Medicare Advantage	10 (8.9)	4 (11.4)	2 (5.0)	3 (17.6)	1 (7.7)	0 (0.0)	3 (5.9)	2 (10.0)	5 (12.2)
Unknown	29 (25.9)	8 (22.9)	11 (27.5)	7 (41.2)	3 (23.1)	0 (0.0)	14 (27.5)	4 (20.0)	11 (26.8)
Baseline comorbidities, n (%)									
Coronary artery disease	7 (6.3)	2 (5.7)	1 (2.5)	4 (23.5)	0 (0.0)	0 (0.0)	4 (7.8)	2 (10.0)	1 (2.4)
Depression	34 (30.4)	10 (28.6)	9 (22.5)	7 (41.2)	5 (38.5)	3 (42.9)	22 (43.1)	4 (20.0)	8 (19.5)
Diabetes insipidus	11 (9.8)	3 (8.6)	3 (7.5)	2 (11.8)	2 (15.4)	1 (14.3)	2 (3.9)	2 (10.0)	7 (17.1)
Diabetes mellitus	22 (19.6)	2 (5.7)	9 (22.5)	6 (35.3)	2 (15.4)	3 (42.9)	9 (17.6)	5 (25.0)	8 (19.5)
Fatigue	29 (25.9)	11 (31.4)	12 (30.0)	2 (11.8)	2 (15.4)	2 (28.6)	10 (19.6)	8 (40.0)	11 (26.8)
Insomnia	15 (13.4)	5 (14.3)	5 (12.5)	3 (17.6)	1 (7.7)	1 (14.3)	7 (13.7)	4 (20.0)	4 (9.8)
Heart failure	8 (7.1)	3 (8.6)	1 (2.5)	2 (11.8)	0 (0.0)	2 (28.6)	4 (7.8)	3 (15.0)	1 (2.4)
Hyperglycemia	20 (17.9)	5 (14.3)	4 (10.0)	6 (35.3)	2 (15.4)	3 (42.9)	11 (21.6)	4 (20.0)	5 (12.2)
Hypersomnia	15 (13.4)	5 (14.3)	5 (12.5)	3 (17.6)	1 (7.7)	1 (14.3)	7 (13.7)	4 (20.0)	4 (9.8)
Hypertension	54 (48.2)	15 (42.9)	17 (42.5)	9 (52.9)	7 (53.8)	6 (85.7)	21 (41.2)	14 (70.0)	19 (46.3)
Hypopituitarism	14 (12.5)	2 (5.7)	9 (22.5)	1 (5.9)	2 (15.4)	0 (0.0)	1 (2.0)	1 (5.0)	12 (29.3)
Pituitary stalk interruption syndrome	15 (13.4)	2 (5.7)	7 (17.5)	0 (0.0)	4 (30.8)	2 (28.6)	0 (0.0)	0 (0.0)	15 (36.6)
Seizures	3 (2.7)	1 (2.9)	1 (2.5)	1 (5.9)	0 (0.0)	0 (0.0)	1 (2.0)	2 (10.0)	0 (0.0)
Sleep apnea	11 (9.8)	0 (0.0)	2 (5.0)	3 (17.6)	3 (23.1)	3 (42.9)	2 (3.9)	3 (15.0)	6 (14.6)
Visual impairments	33 (29.5)	4 (11.4)	14 (35.0)	9 (52.9)	3 (23.1)	3 (42.9)	8 (15.7)	3 (15.0)	22 (53.7)

BMI, body mass index. The baseline period is defined as the year before and including the index insult date. BMI at insult is defined as the BMI assessment preceding the index insult date, with a maximum lookback of 2 months. If there was no BMI record in that window, the first BMI assessment in the 7-day period following the index insult date was used. *BMI <25 kg/m^2. †BMI 25-29.99 kg/m^2. ‡BMI 30-34.99 kg/m^2. §BMI, 35-39.99 kg/m^2. ¶BMI, ≥40 kg/m^2.

Patient Characteristics by BMI at Index Insult and Hypothalamic Insult Type

- More than half of patients (52.7%) were female, and most were white (63.4%). The mean (SD) age was 48.5 (13.5) years. The most common insurance plans at index were commercial (33.0%) and Medicaid (32.1%; Table)
- Most (67%) did not have obesity at the time of the index insult (Figure 2)
- The most commonly observed baseline comorbidities were hypertension (48.2%), visual impairment (29.5%), depression (30.4%), and fatigue (25.9%; Table)
- Among subgroups, more comorbidities were generally seen in patients with more severe obesity, except fatigue, which was most prevalent among patients with overweight (30%). The top comorbidity among patients with trauma-related aHO was depression (43.1%) compared with 20% among patients with tumor-related aHO (Table)
- Specialists were underutilized during baseline; among those with specialist data, 61%, 19%, 19%, and 3% visited neurologists/oncologist, endocrinologists, gastroenterologists, and sleep specialists, respectively

Rapid Weight Gain Following Hypothalamic Obesity

- Within 12 months of hypothalamic insult, an average BMI increase of 17.7% (4.7 BMI points) was observed (n=112)
- A larger magnitude of rapid weight gain was observed among those with tumor radiation–related and trauma-related aHO compared with tumor surgery–related aHO (Figure 3). Those who had overweight at index insult (BMI 25 to <30 kg/m^2) had the most rapid weight gain compared with other BMI groups (Figure 4)
- In total, 71 patients (64%) experienced an increase of at least 1 obesity class. The largest increases were observed among those with BMI <25 kg/m^2 at index insult and those with trauma-related aHO

Figure 2. Baseline Body Mass Index Distribution

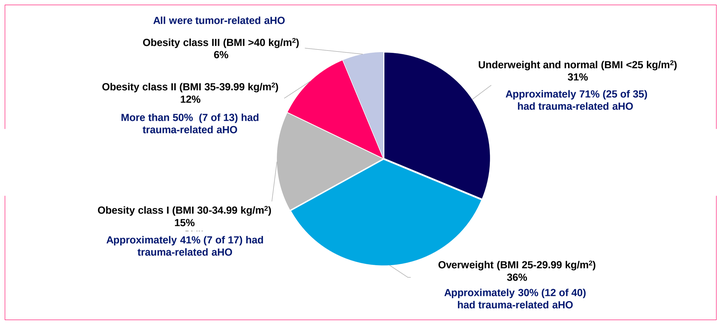


Figure 3. Weight Gain 12 Months After Index Hypothalamic Insult, by Insult Type

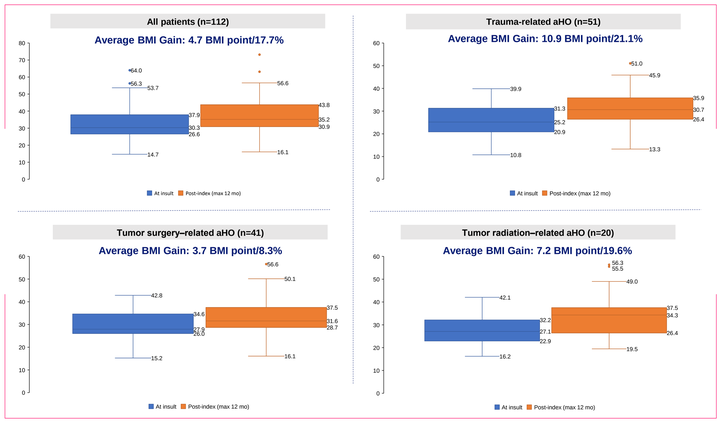
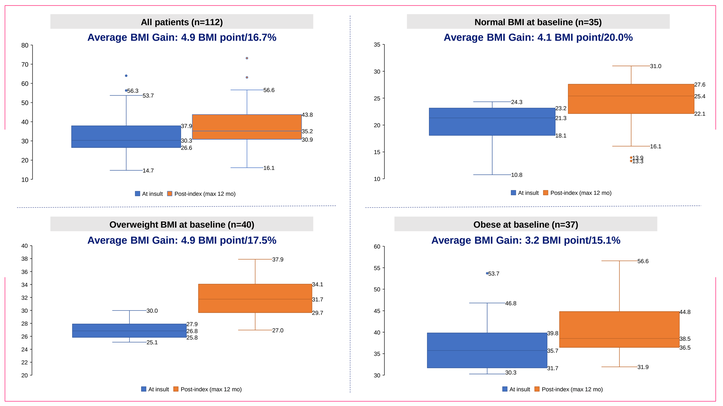


Figure 4. Weight Gain 12 Months After Index Hypothalamic Insult, by Baseline Body Mass Index



Conclusions

- This is the first US real-world study characterizing the accelerated weight gain following hypothalamic insult among adult patients with tumor- and trauma-related aHO
- Patients with aHO were found to have high comorbidities before index insult accompanied by underutilization of relevant specialist care. Following hypothalamic damage, weight gains were more rapid among patients with tumor radiation–related and trauma-related aHO and those who were overweight at the time of hypothalamic insult. These findings highlight the unmet needs in the patient population and the importance of early diagnosis and treatment