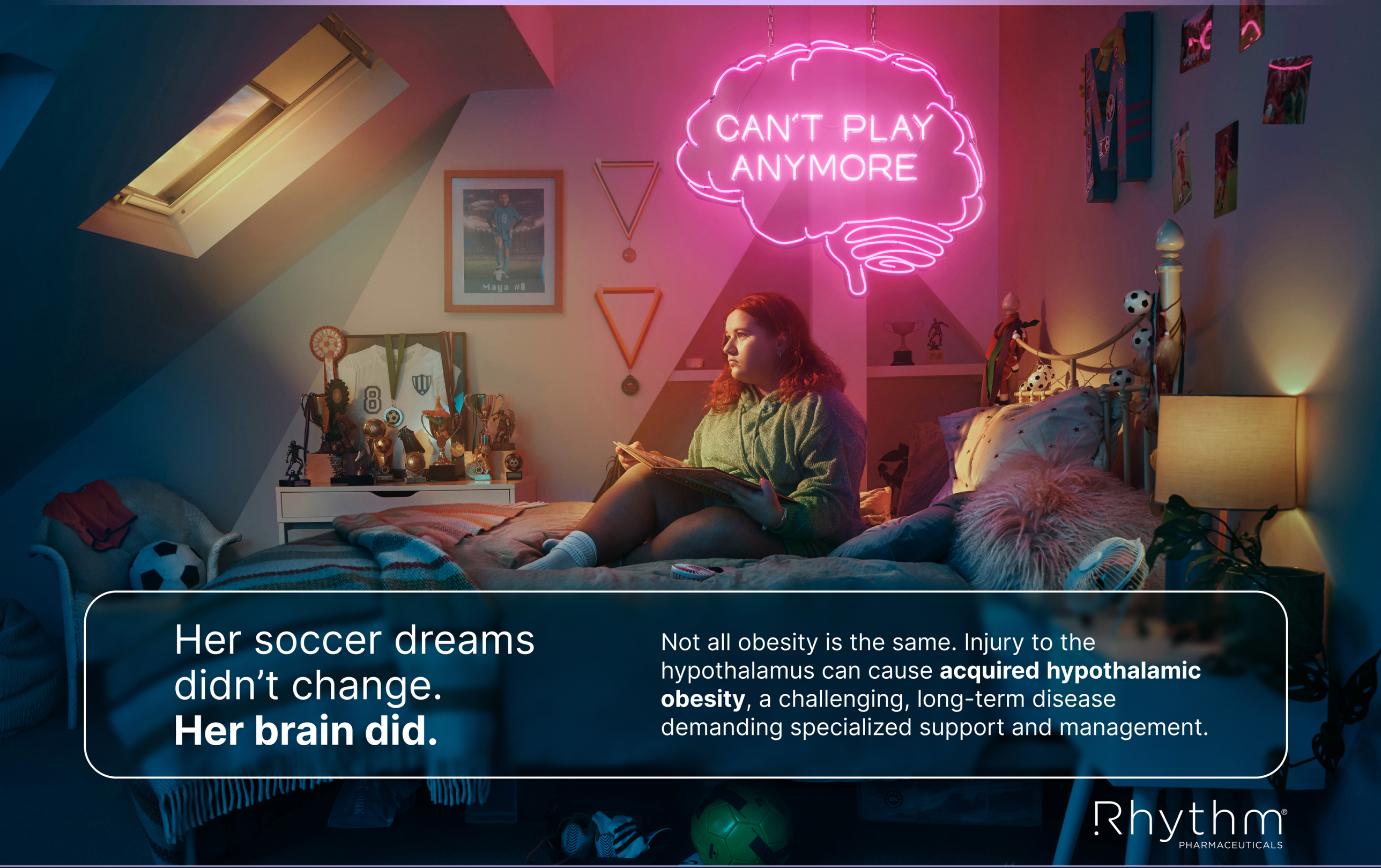


Her soccer dreams didn't change.
Her brain did.

Not all obesity is the same. Injury to the hypothalamus can cause **acquired hypothalamic obesity**, a challenging, long-term disease demanding specialized support and management.

Rhythm® PHARMACEUTICALS

Acquired hypothalamic obesity (HO) is a unique form of obesity caused by injury to the hypothalamus[1–4]

Acquired HO is characterized by accelerated and sustained weight gain.[1–4]

HEALTHY HYPOTHALAMUS

The **hypothalamus plays a key role** in many diverse functions, including regulating[5]:

- **Satiety and hunger**
- **Energy expenditure**

→ **Body weight**

Patients with **injury to the hypothalamus** experience a variety of health concerns, one of which is acquired HO.[5,6]

While HO can be congenital or acquired, **more than 80% of cases are acquired**.[8]

ACQUIRED HYPOTHALAMIC OBESITY

Unlike general obesity, acquired HO is characterized by **distinct factors that contribute to weight gain**[5,7]:

- **Hyperphagia**
- **Decreased energy expenditure**

→ **Accelerated, sustained weight gain**

There are several causes of acquired hypothalamic obesity (HO)[8]

KNOWN COMMON CAUSES[8]:

- **Brain tumors**, including craniopharyngioma, astrocytoma, and macroadenoma of the pituitary
- **Brain tumor treatment**, including surgical resection and radiotherapy

OTHER CAUSES[8]:

- Traumatic brain injury
- Stroke
- Disorders that cause inflammation to the hypothalamus

Know who is at risk—acquired HO occurs in up to **75% of patients with craniopharyngioma** following treatment.[9]

Acquired hypothalamic obesity (HO) has an underlying pathophysiology that distinguishes it from general obesity[1–4]

Acquired HO can occur when hypothalamic injury impairs MC4R pathway function.[1–4]

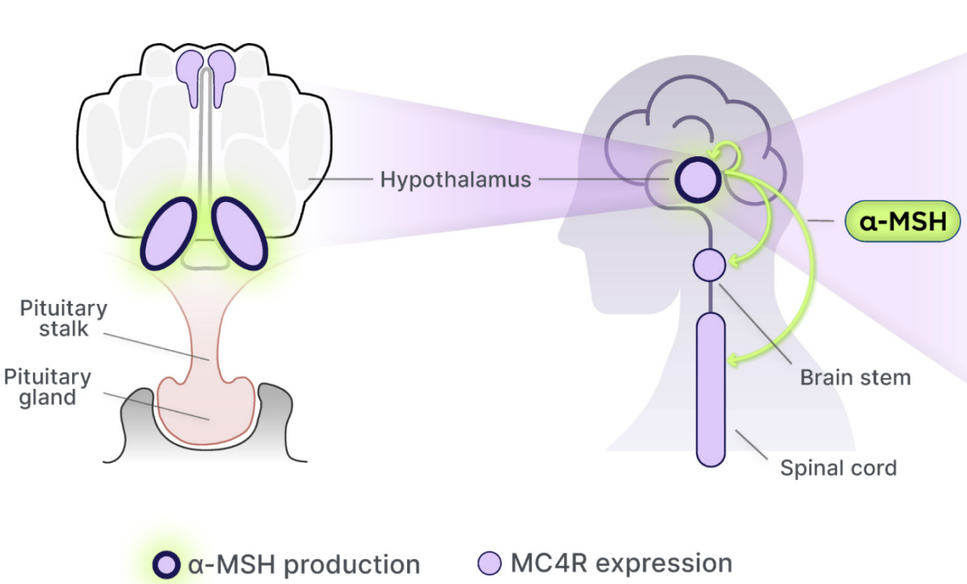
Functional MC4R pathway activity | Impaired MC4R pathway activity

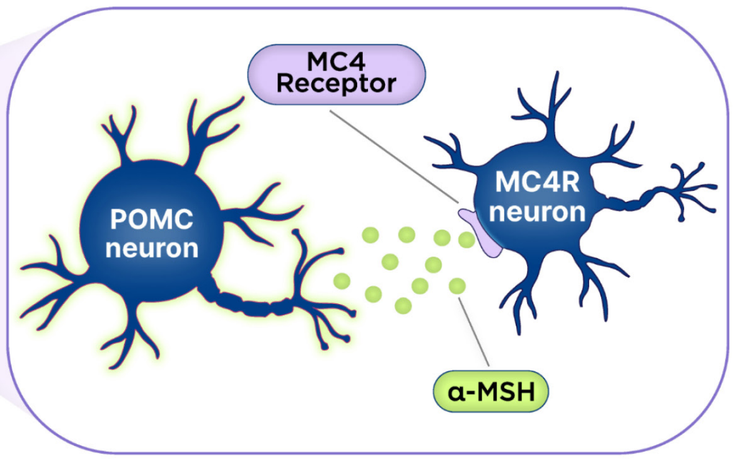
The MC4R pathway regulates hunger, satiety, and energy expenditure.[10–12]

α-MSH is produced in the hypothalamus, near the pituitary gland.

α-MSH from the hypothalamus activates MC4 receptors expressed across the central nervous system.

α-MSH is produced by POMC neurons and binds to MC4 receptors to activate the MC4R pathway.





MC4R activation by α-MSH controls:

Hunger and satiety + Energy expenditure

Result:

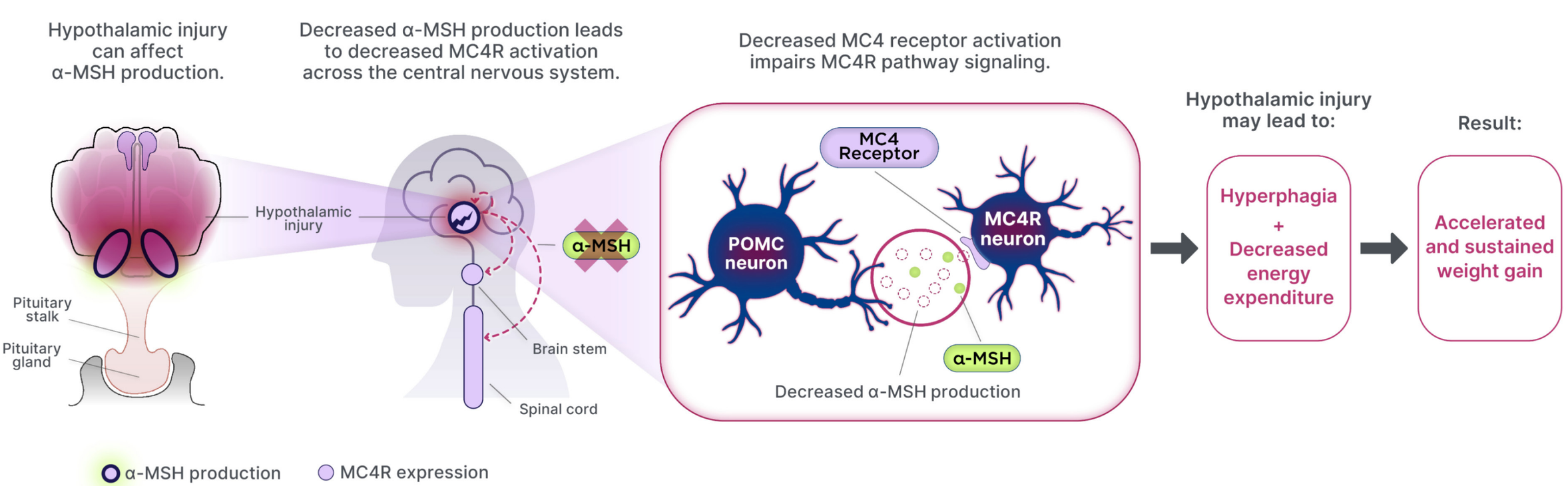
Regulated body weight

Acquired hypothalamic obesity (HO) has an underlying pathophysiology that distinguishes it from general obesity[1–4]

Acquired HO can occur when hypothalamic injury impairs MC4R pathway function.[1–4]

Functional MC4R pathway activity | **Impaired MC4R pathway activity**

Injury to the hypothalamus can disrupt MC4R pathway signaling, ultimately leading to accelerated and sustained weight gain.[1-4,13,14]



Acquired hypothalamic obesity (HO) carries significant, long-term burden for people with hypothalamic injury[14,15]

There is a strong and significant correlation between increased weight and decreased quality of life for patients with acquired HO and their caregivers.[13,14]

Physical burden

Significant burden on patients' and caregivers' day-to-day lives[13,14]:

- Hyperphagia
- Chronic fatigue
- Decreased physical activity
- Weight gain, even in the absence of increased caloric intake

Emotional burden

Distressing emotional and social challenges for patients[13,14]:

- Poor body image perceptions
- Fewer positive social interactions
- Negative impact on mental health
- Frustration due to difficulty losing weight

SEE THE LONG-TERM EFFECTS IN CRANIOPHARYNGIOMA SURVIVORS

TAP TO SEE DATA

Acquired hypothalamic obesity (HO) carries significant, long-term burden for people with hypothalamic injury[14,15]

Acquired hypothalamic obesity is a major risk factor for related morbidity and mortality.[6,15]

> “When you're actively watching your child suffer, it's pretty impactful on [your] wellbeing. It’s... the grief, the sadness, the fear for **what this means for his future health, both physical health and mental health.**”
>
> – CAREGIVER OF AN INDIVIDUAL LIVING WITH ACQUIRED HO

LONG-TERM EFFECTS OF OBESITY-RELATED SEQUELAE IN CRANIOPHARYNGIOMA SURVIVORS[16–18]

- **52%** Nonalcoholic fatty liver disease
- **40%** Hypertension
- **46%** Sleep apnea
- **34%** Glycemic disturbance
- **43%** Dyslipidemia
- **22%** Cardiovascular disease

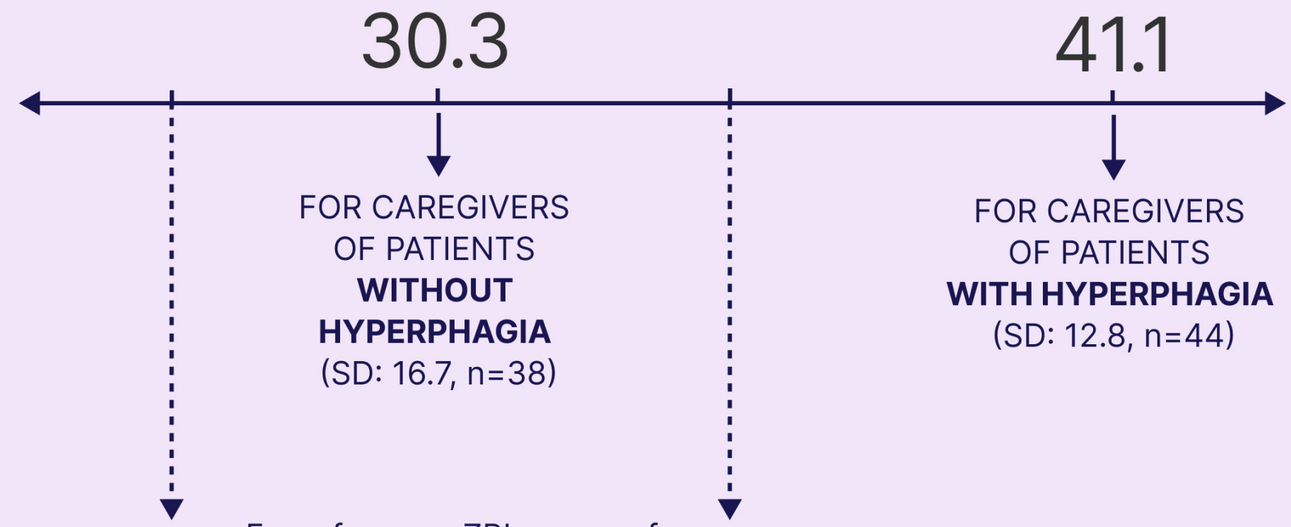
Hyperphagia contributes significantly to patient and caregiver burden in acquired hypothalamic obesity (HO)[13]

Hyperphagia is a chronic, pathological, insatiable hunger and impaired satiety accompanied by persistent and abnormal food-seeking behavior.[5,7]

of patients with acquired HO reported they struggle with the burden of hyperphagia.[13]

> "**Food ruled my life** and still does to a certain degree... it's a lot of grief and struggle in my everyday life."
>
> – INDIVIDUAL LIVING WITH ACQUIRED HO

MEAN BURDEN SCORES (ZBI) REPORTED BY CAREGIVERS OF CRANIOPHARYNGIOMA PATIENTS*,[13]



For reference, ZBI scores of **23.7 for cancer** caregivers and **36.8 for Alzheimer's disease** caregivers have been reported[19]

*Based on 82 self-identified caregivers of hypothalamic-pituitary brain tumor survivors responding in an online survey to the Zarit Burden Interview, which assesses the perceived burden experienced by caregivers of individuals with chronic illnesses or disabilities; a higher score indicates a greater level of caregiver burden.

Screening for acquired hypothalamic obesity (HO) is critical in cases of hypothalamic injury

CLINICAL DIAGNOSIS[1,6,7,9,20,21]

A clinical diagnosis of acquired HO is characterized by **accelerated and sustained weight gain, most often within the initial 6 to 12 months** following injury to the hypothalamus.

VARIABLE PRESENTATION[7,22]

Acquired HO can have variable time to onset and progression of weight gain due to **type, location, and extent of hypothalamic injury**.

CONFOUNDING FACTORS

Recognizing acquired HO may be confounded by temporary weight gain from **medications or hormone replacements**.

Many patients may not be aware of acquired HO as a risk following hypothalamic injury or may only be focused on other post-treatment concerns.

SEE SIGNS AND SYMPTOMS THAT CAN INDICATE ACQUIRED HO

TAP TO SEE SIGNS

About Acquired HO | Causes | Disease Mechanism | Obesity Burden | Hyperphagia Burden | Diagnosis | Management | Patient Support | Summary

Screening for acquired hypothalamic obesity (HO) is critical in cases of hypothalamic injury

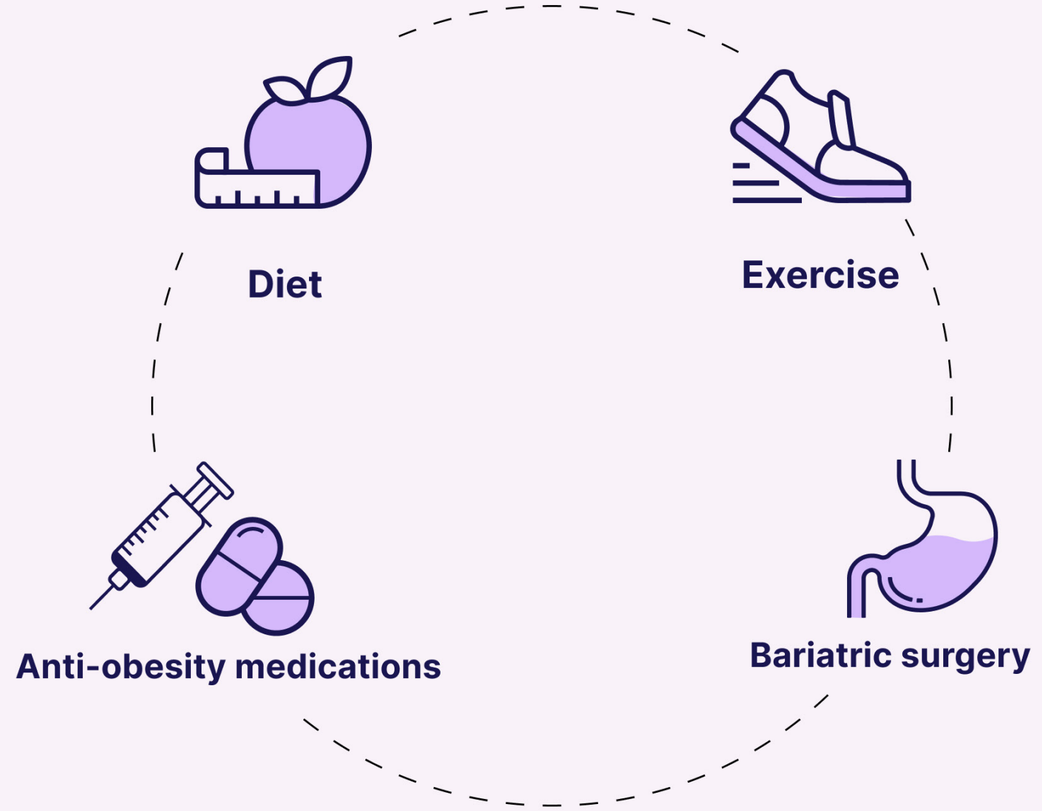
Minimize diagnostic delays due to competing medical needs or other confounding factors. Stay alert for signs that could indicate acquired HO at different stages.[7,13,23]

SCREEN ALL PATIENTS	MONITOR PROACTIVELY IN NEW PATIENTS	FOLLOW UP WITH EXISTING PATIENTS
Screen patients with a history of hypothalamic injury, including from[5,7,13,23]:	**Early signs and symptoms** that can help identify patients with acquired HO include[5,7,13,23]:	**Patients with a past brain injury** may[1,7,12]:
• Brain tumors • Brain tumor treatment • Traumatic brain injuries • Stroke	• Accelerated and sustained weight gain, even in the absence of increased caloric intake • Increased hunger or hyperphagia • Decreased physical activity • Increased levels of fatigue or daytime sleepiness	Experience persistent obesity that is resistant to calorie restriction, exercise, or other weight loss interventions.

There is a critical need to recognize the urgency to diagnose and manage acquired hypothalamic obesity (HO) due to its impact on patients and families[1,6,7,13-15]

Patients may experience short-term weight loss with lifestyle modifications, anti-obesity medications, or surgery, but **these approaches have shown limited efficacy in producing sustained results in acquired HO.**[1,6,7,9,20,21,24]

CURRENTLY THERE IS NO FDA-APPROVED TREATMENT SPECIFICALLY INDICATED FOR ACQUIRED HO.[6,25,26]



While acquired HO can be challenging to manage, **early identification and proactive intervention** may help to **slow the progression of weight gain** and help patients better understand their disease.[8,16]

Connect patients and family members with someone who understands acquired hypothalamic obesity (HO) and its challenges

Rhythm InTune

A program that provides one-on-one educational support for people with acquired HO and their family members.

Patient Education Managers* are trained to:

- Provide resources, education, and information tailored to the **unique needs of patients with acquired HO**
- Help patients and family members connect to a community of others living with acquired HO

Many patients may be unprepared for the impact of acquired HO, so accessing tailored resources and 1:1 education can make a meaningful difference.

*Patient Education Managers are employees of Rhythm Pharmaceuticals and do not provide medical care or advice. We encourage patients to always speak to their healthcare providers regarding their medical care.

Acquired hypothalamic obesity (HO) is a unique form of obesity caused by hypothalamic injury that impairs MC4R pathway function.

Weight gain and hyperphagia from acquired HO contribute significantly to patient and caregiver burden.

Promote early identification and education in your practice:

- Discuss signs and symptoms to watch out for with your patients
- Screen all patients with hypothalamic injury
- Connect patients and caregivers with one-on-one educational support

SEE REFERENCES

Rhythm® PHARMACEUTICALS

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