Acquired hypothalamic obesity:
Definition and diagnostic criteria

Acquired hypothalamic obesity (aHO) is an accelerated and sustained weight gain resulting from physical injury or structural abnormality of the hypothalamus with MC4R pathway disruption and other hypothalamic functional impairment[1,2]

In aHO, hyperphagia (pathological, insatiable hunger) and decreased energy expenditure caused by MC4R pathway disruption lead to accelerated and sustained weight gain[1]

aHO aetiology

The root cause of aHO clearly contrasts with that of general obesity, which is polygenic in nature.[1] aHO should be recognised as a distinct clinical disease of hypothalamic impairment with consistent clinical features and therapeutic needs regardless of the underlying aetiology[2]

aHO is a rare neuroendocrine disease caused by hypothalamic MC4R pathway disruption:

Rare neuroendocrine diseases[1]

Rare hypothalamic MC4R pathway diseases (ICD-10-CM diagnosis code E88.82)[1*]

Physical injury or structural abnormality of the hypothalamus, or clinical hypothalamic functional impairment caused by:

- Tumours and/or tumour treatment[1]
- Traumatic brain injury[1]
- Inflammation, infection, stroke, and other injuries to the hypothalamus[3]
- Anatomical defects[4,5]

Acquired hypothalamic obesity

Timely diagnosis of aHO is important as obesity due to accelerated and sustained weight gain contributes to the development of a large range of life-threatening complications[2]

*ICD-10-CM code covers obesity due to MC4R pathway diseases including those with obesity due to disruption of the MC4R pathway or obesity due to a genetic aetiology; it is within the endocrine and metabolic diseases classification and not obesity.

Diagnostic criteria of aHO[1,2]

The presence of two core features can drive suspicion of MC4R pathway disruption*

Physical injury or **structural** abnormality of the hypothalamus or **clinical hypothalamic functional impairment**

Monitor for

One should trigger active **monitoring/ searching** for the other

Search for

Accelerated and sustained weight gain associated with the hypothalamic injury or impairment

MC4R pathway disruption can lead to obesity and an aHO diagnosis

The following features can support the identification of hypothalamic injury that might lead to a diagnosis of aHO:

- Hyperphagia (pathological, insatiable hunger)
- Fatigue, reduced physical capacity and loss of initiative
- Pituitary hormone deficiencies
- Mild hyperinsulinism
- Impaired quality of life
- Temperature dysregulation
- Behavioural changes

Not all features need to be present and variability among patients should be taken into account upon evaluation

Consequences

- Abnormal body composition
- Obstructive sleep apnoea syndrome
- Cardiovascular complications
- Excessive daytime sleepiness
- Reduced physical capacity
- Cognitive, behavioural, emotional, and psychosocial consequences
- Arthralgia

*The absence of physical injury, structural abnormality or clinical hypothalamic functional impairment, or gradual vs accelerated weight gain without linkage to a clear cause, should prompt reconsideration of the aHO diagnosis

Regardless of the aetiology, patients with aHO share MC4R pathway disruption leading to similar symptoms, clinical outcomes and therapeutic goals including management of hyperphagia, and resolution of the resulting accelerated weight gain

aHO, acquired hypothalamic obesity; MC4R, melanocortin-4 receptor.

References: 1. Van Santen HM, et al. *Diabetes Obes Metab.* 2026;10.1111/dom.70725; 2. Müller HL, et al. *Front Endocrinol.* 2026:10.3389/fendo.2026.1798619; 3. Hochberg I, et al. *Obes Rev.* 2010;11:709–721; 4. Cerbone M, et al. *E Clinical Medicine.* 2020:10.1016/j.eclinm.2019.11.017; 5. Nannette G, et al. *J Clin Endocrinol Metab.* 2023;108(2):323–330.

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