Definition and Diagnostic Criteria for Acquired Hypothalamic Obesity: Global Expert Panel Consensus

#370

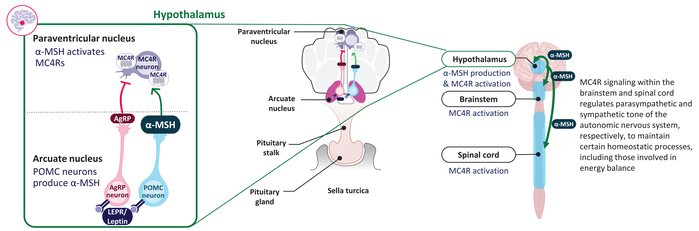
Christian L. Roth[1*], Ashley Shoemaker[2*†], Hiroshi Arima[3], Lewis Blevins[4], Daniel C. Bowers[5], Odelia Cooper[6], Mehul T. Dattani[7], Ilene Fennoy[8], Johan P de Graaf[9], Jill Hamilton[10], Mohamad Maghnie[11], Brent Masel[12], Hermann L. Müller[13], Christine Poitou[14], Amy Wood[15], Kevin C.J. Yuen[16], and Hanneke M. van Santen[17*]

*Co-chairs
†Author affiliation at the time the modified Delphi process was conducted. Current affiliation: Rhythm Pharmaceuticals, Inc.

[1]Seattle Children's Hospital, University of Washington, Seattle, WA, USA, [2]Vanderbilt University Medical Center, Nashville, TN, USA, [3]Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan, [4]University of California, San Francisco, CA, USA, [5]UT Southwestern Medical Center School, [6]Cedars-Sinai Medical Center, Los Angeles, CA, USA, [7]University College London Great Ormond Street Institute, of Child Health, Genetics and Genomic Medicine Programme, London, UK, [8]Columbia University Irving Medical Center, NY, NY, [9]Dutch Pituitary Foundation, Department of Endocrinology, Leiden University Medical Center, The Netherlands, [10]University of Toronto, Toronto, ON, [11]IRCCS Istituto Giannina Gaslini, University of Genova, [12]University of Texas Medical Branch, Galveston, TX, USA, [13]University Children's Hospital, Carl von Ossietzky Universität, Klinikum Oldenburg AöR, Oldenburg, [14]Sorbonne Université, Inserm, Nutrition and Obesities, Systemic Approaches NutriOmique Research Group, Paris, France, [15]Raymond Wood Foundation, 16Barrow Pituitary Center, Barrow Neurological Institute, Phoenix, AZ, USA,[17]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands and the Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Background

- Acquired hypothalamic obesity (HO) is a rare neuroendocrine disease characterized by abnormal weight gain following structural or functional injury to the hypothalamic-pituitary region.[1-3] Its pathophysiology differs from general obesity.



- Recognition of acquired HO is complicated by the heterogeneity of hypothalamic injury, with differences in injury location, etiology, and severity producing diverse clinical features of hypothalamic dysfunction, variable comorbidity profiles, and differing patterns of weight gain.
- The absence of a standardized definition and diagnostic criteria for acquired HO may lead to mis- or delayed diagnosis and suboptimal management of obesity and outcomes.

Objective

To establish an international consensus definition & diagnostic framework for acquired HO

Methods

1. Convene a 17-member modified Delphi consensus panel (14 voting panelists; three non-voting co-chairs)
2. SLR under direction from co-chairs
3. Co-chairs develop SLR-informed statements
4. **Round 1 survey** (5-point Likert scale questionnaire)
   - 1 Analyze survey results
   - 2 Collate questions that have not reached consensus to be sent back for Round 2
   - 3 Compare individual responses with aggregate panel responses in an anonymized report
5. **Round 2 survey** (5-point Likert scale questionnaire; allowed qualitative comments)
   - 1 Analyze survey results
   - 2 Collate questions that have not reached consensus and qualitative comments for discussion in the whole-panel virtual meeting
6. **Whole-panel virtual meeting**

Survey consensus definitions; 5-point Likert scale questionnaire

Strong consensus	Consensus	No consensus
≥90% agreement	≥75% agreement	<75% agreement

Diagnostic Framework for Acquired HO

DEFINITION

Acquired HO or overweight is defined as weight gain following hypothalamic-only or hypothalamic-pituitary injury, which can occur in both children & adults

Often accelerated and sustained if left untreated • Distinct from general obesity

DIAGNOSTIC CRITERIA

Requires BOTH evidence of injury AND a characteristic pattern of weight gain

EVIDENCE OF INJURY

1 Injury diagnosis or history

Known or suspected hypothalamic-only or hypothalamic-pituitary injury

And/ Or

2 Hypothalamic dysfunction

Pituitary deficiency, hyperphagia, autonomic dysfunction, and/or supportive features

WEIGHT-GAIN TRAJECTORY

1 Rapid / steep

Significant weight gain over a short period after injury

2 Slow / steady

A gradual weight-gain trajectory

3 Delayed onset

Stable initial phase followed by later-onset weight gain

Imaging may support diagnosis but is NOT required

- Characteristic acquired HO weight-gain trajectories may occur across multiple etiologies, although supporting evidence remains limited beyond brain tumors
- Established region-specific reference standards used to define overweight or obesity can be applied in patients with acquired HO; however, diagnosis additionally requires condition-specific criteria such as hypothalamic injury and one of the weight-gain patterns

Supportive Diagnostic Considerations

Not all patients with hypothalamic-only or hypothalamic-pituitary injury develop acquired HO, and **pituitary deficiency is not a prerequisite** for diagnosis.

Within 3 months of hypothalamic-pituitary tumor injury, mild transient weight gain may reflect hormone deficiency and/or steroid therapy, whereas acquired HO weight gain is **sustained and steeper**.

Pre-existing general obesity **does not exclude** acquired HO if a distinct change in weight trajectory follows the injury.

Abbreviations: α-MSH, alpha-melanocortin stimulating hormone; Gy, gray; HO, hypothalamic obesity; MC4R, melanocortin-4 receptor; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR, systematic literature review; TBI, traumatic brain injury.

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Editorial assistance was provided by Syneos Health and funded by Rhythm Pharmaceuticals, Inc. under the direction of the authors

Author disclosures: AS is currently an employee of Rhythm Pharmaceuticals. AS was an employee of Vanderbilt University during the development of the consensus work which was finished in April 2026 and she joined Rhythm in July 2026. While at Vanderbilt University she received institutional research support from Rhythm Pharmaceuticals, Soleno Therapeutics, Novo Nordisk, and Aardvark Therapeutics; CLR has received institutional research support for clinical trials from Rhythm Pharmaceuticals and has served as an advisor for Rhythm Pharmaceuticals. HA has received reimbursement of travel expenses and lecture honoraria from Rhythm Pharmaceuticals. LB has received honoraria from Rhythm Pharmaceuticals;DCB has no conflicts of interest to declare. OC has received honoraria for lectures from Rhythm Pharmaceuticals, Novo Nordisk, and Eli Lilly; MTD has received grant funding from Rhythm Pharmaceuticals, and Soleno; has contributed to an advisory board meeting for Rhythm Pharmaceuticals; IF has received honoraria for clinical activities and lectures from Rhythm Pharmaceuticals; JPdG The Dutch Pituitary Foundation (nl.2PAS) pursuant to its statutes, has received grant funding from Rhythm Pharmaceuticals; JH has received honoraria from Pfizer, Ipsen, Novo Nordisk, Eisai, and Viatris; MM has received honoraria from Pfizer and Ipsen; BM has received honoraria from Pfizer, Novo Nordisk, Eisai, and Viatris; HLM has received honoraria from Pfizer, Ipsen, Eisai, and Novo Nordisk; CP has received honoraria from Pfizer and Novo Nordisk; AW has received honoraria from Pfizer and Recordati; KCJY has received honoraria from Pfizer and Recordati; HMvS has received honoraria from Pfizer and Ferring; The Dutch Pituitary Foundation (nl.2PAS) pursuant to its statutes, has received grant funding from Pfizer and Ferring; Pediatrieportaal Samenwerking Medicijnen (PSM), which is a collaboration between multiple patient organizations and pharmaceutical companies in The Netherlands; JH has received institutional support for industry-sponsored studies from Eli Lilly, Novo Nordisk, Pfizer, and Rhythm Pharmaceuticals; has received investigator-initiated research grants from the Foundation for Prader Will Research, Mead Johnson, National Institutes of Health, and Sunlife Foundation; and has participated in advisory boards with Rhythm Pharmaceuticals; MM has received compensation for participation in advisory boards from Ascendis, BioMarin, Edsive, Merck, Novo Nordisk, Pfizer, and Sandoz; has served as a consultant for BioMarin, Merck, Novo Nordisk, Pfizer, and Sandoz; has received grants from Merck, Novo Nordisk, and Pfizer; and has served as a speaker for BioMarin, Merck, Novo Nordisk, Pfizer, and Sandoz; BM has served as an advisor for Rhythm Pharmaceuticals. He has served on an advisory board for Novo Nordisk; HLM has received reimbursement of participation fees for scientific meetings and continuing medical education events, and reimbursement of travel expenses and lecture honoraria, from Rhythm Pharmaceuticals, Ipsen, Novo Nordisk, Pfizer, Eisai, and Viatris; CP has received honoraria for lectures from Rhythm Pharmaceuticals, Novo Nordisk, Eli Lilly, Pfizer, Ipsen, Viatris, and Boehringer Ingelheim; AW has received honoraria for lectures from Rhythm Pharmaceuticals, Pfizer, Ipsen, Eisai, and Recordati, as well as support to attend conferences from Rhythm Pharmaceuticals, and Soleno Therapeutics; CP has also received institutional research support from Rhythm Pharmaceuticals; AW is the Executive Director and Founder of the Raymond A. Wood Foundation; KCJY has received institutional support for clinical trials sponsored by Barrow Neurological Institute from Ascendis, Novo Nordisk, Recordati, and Sparrow; has received occasional consultant fees from Ascendis, Camurus, Chiesi, Corcept, Crinetics, Elon, Marea Therapeutics, Novo Nordisk, Rhythm Pharmaceuticals and Recordati; and has served as a speaker for Ascendis, Camurus, Crinetics, and Recordati; HMvS is local primary investigator of the Transcend Study (funded by Rhythm Pharmaceuticals); has received funding from Novo Nordisk, Pfizer, and Rhythm Pharmaceuticals for the organization of the ESPE Science Symposium and the 6th Craniopharyngioma Post-graduate Course; has received reimbursement of travel expenses for a scientific meeting by Rhythm Pharmaceuticals; and has received funding for research projects from Pfizer and Rhythm Pharmaceuticals.

Factors Associated with the Development of Acquired HO

Hypothalamic damage‡

- Bilateral or posterior hypothalamic injury, or unilateral injury involving critical mediobasal hypothalamic nuclei
- Moderate to severe traumatic brain injuries (TBI) involving midline brain structures, including the mediobasal hypothalamic-pituitary region
- Vascular injury or other events involving the hypothalamic-pituitary region

Note: The location and extent of hypothalamic injury are intended to explain disease biology rather than establish diagnostic criteria. In routine clinical practice, involvement of specific hypothalamic structures cannot be reliably confirmed using standard neuroimaging.

Tumor type

- Presence of the adamantinomatous (as opposed to papillary) craniopharyngioma subtype

Increased intracranial pressure

- Increased intracranial pressure or mass effect at presentation, including obstructive hydrocephalus

Surgery

- Tumor recurrence and an increasing number of tumor interventions
- Gross total resection, particularly with greater preoperative hypothalamic involvement

Higher radiation dose

- Higher radiation dose to the hypothalamic region (e.g., >51 Gy)

Familial predisposition and pre-existing overweight or obesity may increase the degree of obesity after injury

Clinical Importance of the Framework

- Acquired HO is a distinct, rare neuroendocrine disease that arises from hypothalamic injury and cannot be fully understood through the framework of general obesity.
- This international expert consensus establishes the first standardized definition and diagnostic criteria based on the combination of hypothalamic injury and a compatible weight-gain trajectory.
- Adoption of this framework is aimed at improving recognition of acquired HO across specialties, resulting in earlier diagnosis and targeting the underlying drivers of disease to support more precise, disease-specific multidisciplinary patient care and management.

Strengths & Limitations

- Integration of an SLR with a modified Delphi process
- International and multidisciplinary composition of the expert panel, including patient advocacy perspectives and applicability across pediatric and adult populations

- Available evidence is largely limited to retrospective studies, case reports, and cross-sectional analyses
- Non-tumor etiologies, standardized imaging criteria, and risk modifiers remain underrepresented or rely on expert clinical experience

References: 1. van Santen HM, Shoemaker AH, Dattani MT, et al. Defining Acquired Hypothalamic Obesity: An Expert Call for Unified Diagnosis and Therapeutic Action. *Diabetes Obes Metab*. Jun 2026;28(6):4437-4441. 2. Müller HL, Tauber M, Lawson EA, et al. Hypothalamic syndrome. *Nat Rev Dis Primers*. Apr 21 2022;8(1):24. 3. Roth CL, McCormack SE. Acquired hypothalamic obesity: A clinical overview and update. *Diabetes Obes Metab*. Apr 2024;26 Suppl 2:34-45.