A Q&A WITH PROFESSOR PAUL DIMITRI

Acquired hypothalamic obesity: Expert perspectives on recognition, burden, and management

Professor Paul Dimitri is a Professor of Child Health and a Consultant in Paediatric Endocrinology at Sheffield Children's Hospital, UK, with extensive experience in managing children and young people with hypothalamic and pituitary axis tumours.

Acquired hypothalamic obesity 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] It can arise from a range of aetiologies, including tumours and their associated treatments, traumatic brain injury, infections, inflammation, stroke and anatomical defects, among others.[3–7] In addition to the accelerated weight gain, the key clinical features include hyperphagia (pathological, insatiable hunger) and reduced energy expenditure which are driven by disruption of the MC4R pathway.[1,8]

In this expert Q&A, Professor Paul Dimitri highlights the clinical features, underlying mechanisms, and management challenges of acquired hypothalamic obesity. In clinical practice, accelerated and sustained increases in BMI in individuals following physical injury or structural abnormality of the hypothalamus may warrant consideration of acquired hypothalamic obesity.[9,10] Onset is variable, with weight gain being reported anywhere from weeks to 3 years following hypothalamic damage, and in some cases, it may even be observed before the underlying aetiology is diagnosed.[1,11–14]

Management is complex, as hypothalamic functional impairment can lead to a combination of neuroendocrine defects that often require polytherapy.[10,15,16] This highlights the need for holistic, multidisciplinary management and ongoing support to address treatment burden and complication management.[17] Increasing awareness and early recognition are critical to enable timely intervention to limit weight gain and manage associated complications.[1,18]

Below, Professor Dimitri addresses some of the key questions clinicians may have when encountering patients at risk of acquired hypothalamic obesity.

Q: What is acquired hypothalamic obesity, and what are the key aetiologies clinicians should be aware of?

Acquired hypothalamic obesity is an accelerated and sustained weight gain resulting from physical injury or functional damage to key hypothalamic nuclei responsible for energy homeostasis.[1,2,10] This makes it fundamentally different from general obesity, which reflects complex interactions between behaviour, environment, and polygenic risk.[19]

Acquired hypothalamic obesity is driven by direct disruption of central neuroendocrine pathways that regulate hunger, satiety, autonomic output, and metabolic rate.[20–22] Damage to key regions such as the arcuate nucleus, ventromedial hypothalamus, dorsomedial hypothalamus, and paraventricular nucleus impairs melanocortin signalling, leptin responsiveness, sympathetic tone, and brown adipose tissue thermogenesis.[1,8] The result is a characteristic phenotype of hyperphagia, impaired satiety signalling, reduced sympathetic activity, decreased resting energy expenditure, and unopposed parasympathetic drive, all of which promote accelerated and sustained weight gain.[1,2,8]

In children and young people, the most reported aetiologies are (supra)sellar tumours, particularly craniopharyngiomas, which frequently invade or compress hypothalamic structures.[1,23–26] Hypothalamic damage can also occur following tumour surgical resection, even when surgery is meticulous.[3,4] Some of these tumours also require cranial radiotherapy, now most commonly proton beam therapy, which can induce delayed hypothalamic functional impairment through radiation scatter.[3,4,27]

Less commonly, acquired hypothalamic obesity can result from severe traumatic brain injury, central nervous system infections, inflammatory diseases, or vascular insults affecting the hypothalamus.[3,10]

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Q: Do factors such as the location or extent of hypothalamic damage influence the likelihood of developing acquired hypothalamic obesity?

There is no doubt that both the location and the extent of hypothalamic damage influence the risk of developing acquired hypothalamic obesity. Specific hypothalamic pathways involved in satiety and energy regulation are located within the arcuate nucleus, ventromedial hypothalamus, dorsomedial hypothalamus, and paraventricular nucleus.[1,8]

When damage involves medial or posterior hypothalamic regions, the risk of acquired hypothalamic obesity is higher.[4,7] We see that more extensive or bilateral lesions are associated with more accelerated and sustained weight gain.[7] While there is some evidence suggesting tumour size alone may not be directly predictive, my experience is that the more extensive the tumour, the more extensive the damage, the more likely you are of developing acquired hypothalamic obesity.[7]

Treatment modality also matters. Neurosurgery to these sensitive regions can result in direct structural injury to the hypothalamus therefore increasing the risk of acquired hypothalamic obesity. Also, radiotherapy itself can cause delayed hypothalamic functional impairment over time.[3,4,27]

Importantly, the aetiology is less important than the impact on the hypothalamus. If any process affects these key hypothalamic regions and pathways, it will most likely increase the risk of acquired hypothalamic obesity.[7,10]

Q: What are the key clinical features of acquired hypothalamic obesity?

The key clinical feature of acquired hypothalamic obesity is accelerated and sustained weight gain,[10] which often begins soon after hypothalamic damage. In many cases, this weight gain is significant and aggressive.[1,8,12–14] However, I am increasingly seeing patients with a more insidious onset of weight gain that later accelerates, suggesting that acquired hypothalamic obesity exists on a spectrum.[10]

The weight gain is driven by two principal mechanisms. One is hyperphagia due to impairment in satiety and the second is a marked reduction in resting metabolic rate and overall energy expenditure.[1,2] When hypothalamic circuits regulating hunger and satiety are disrupted, patients experience insatiable hunger that is difficult to suppress.[1,2] They may feel hungry shortly after eating, wake during the night to seek food, and experience constant intrusive thoughts about food.[28]

Accelerated weight gain, particularly within the first year of hypothalamic damage, should be considered a red flag especially when weight gain occurs irrespective of calorie intake.[9,10]

There can also be more subtle features. These include reduced activity levels, increased fatigue, and sleep disturbance. Some patients may report temperature dysregulation which, while less common, reflects the role of the hypothalamus in regulating body temperature.[8,29,30] and that acquired hypothalamic obesity is part of a wider complication known as hypothalamic syndrome, although classed as a separate clinical entity.[10]

Reduced energy expenditure continues to play an important role in ongoing weight gain.[1] Patients have a reduced basal metabolic rate and reduced energy expenditure, meaning they burn fewer calories at rest and throughout the day.[1,28] This can make weight management more challenging.[1]

Q: How do clinical features such as hyperphagia, reduced energy expenditure, and accelerated weight gain affect patients' daily lives?

Acquired hypothalamic obesity is an extremely challenging and distressing disease.[31] This is not just about weight gain.[31] Patients experience constant pathological, insatiable hunger that dominates daily routines and interferes with sleep. Food becomes central to their thoughts.[28,32]

For children, this impacts school life, not just in terms of schoolwork but also participation in physical and extracurricular activities.[28,33] For adults, it affects work and daily life.[28] For both children and adults, it has a clear impact on social activities, compounded by fatigue, reduced stamina, and physical limitation.[28,33]

The emotional impact is profound and includes frustration, distress, and significant effects on mental health. Overall quality of life is markedly reduced.[33–35]

The disease also places a considerable burden on families and caregivers.[28] Daily activities such as mealtimes or social occasions become difficult to manage and caring for a child with significant weight gain can be physically demanding. The emotional strain on families is substantial.[28,33]

Q: Do all patients present with the same clinical features?

No, they do not.[4,9] Some patients experience pronounced hyperphagia, increased food intake and persistent food seeking behaviour, while others gain substantial weight despite normal or even restricted calorie intake due to profoundly reduced energy expenditure.[1,3,9,28]

In the most severe cases, weight gain is accelerated and sustained, with body mass index rising steeply over a short period.[9,10] However, there is variability in the degree of accelerated weight gain which likely reflects differences in the extent of hypothalamic damage and the specific hypothalamic nuclei affected.[1,8]

Associated features such as sleep disturbance, behavioural changes, and pituitary dysfunction provide important contextual clues and should prompt clinicians to consider hypothalamic involvement.[10]

Q: Why do conventional lifestyle interventions often have limited effectiveness in acquired hypothalamic obesity?

The underlying drivers of acquired hypothalamic obesity are pathophysiological. Hyperphagia is driven by impaired satiety signalling following hypothalamic damage, and energy expenditure and resting metabolic rate are profoundly reduced.[1,10,36]

Even with calorie restriction and increased physical activity, weight loss is physiologically very difficult to achieve.[8,28] Autonomic dysfunction further promotes energy storage rather than fat breakdown,[8] and fatigue and sleep disruption reduce both the capacity and motivation for physical activity.[33,37]

As a result, lifestyle interventions do not have the same positive impact as they do in general obesity.[28]

Q: Where are the biggest gaps in current clinical pathways or support structures?

There are several important gaps. Early identification and routine monitoring protocols are not consistently in place, we need routine monitoring protocols to ensure that acquired hypothalamic obesity is picked up early, so that relevant interventions can be initiated at a much earlier stage.[1,10,18] Access to specialised multidisciplinary teams often varies, and patients with so called benign brain tumours often do not receive the same level of coordinated care as those treated within oncology services,[38] which includes intervention from a psychologist or neuropsychologist, dietician, physiotherapist, occupational therapist and community outreach support.[39]

There also needs to be sufficient ongoing and long-term psychological and social support for families, with concentrated and targeted support in the first 6 to 12 months due to the significant and long term burden.[33] Acquired hypothalamic obesity is currently extremely difficult to treat, and management is a long journey.[8,28] Transition from paediatric to adult care also represents a vulnerable period that requires structured planning and continuity.[40]

Finally, there remains a need for more effective and evidence based pharmacological options to support long term management.[3,4,28,36]

Q: Is there a common misconception about acquired hypothalamic obesity among clinicians that you think is particularly important to challenge or clarify?

One of the most common misconceptions is that acquired hypothalamic obesity can be easily managed with lifestyle interventions. That simply is not the case.[28] This is an incredibly difficult disease to manage, and there is an expectation that if you just eat less and exercise more, you are going to lose weight.[28]

Patients and families are often doing everything they possibly can. Many children are on heavily calorie-restricted diets, and despite this, the accelerated weight gain continues.[28] This is not about poor behaviour or excessive eating in the conventional sense. This is energy dysregulation driven by hypothalamic damage.[1,28]

Another misconception is that families or caregivers are overfeeding their children. In reality, families are often trying desperately to control calorie intake, but accelerated weight gain still occurs.[28]

There is also a perception that patients are not motivated to exercise. Many patients are unable to exercise because of profound fatigue, reduced energy expenditure, sleep disruption, pituitary dysfunction, or physical limitation due to weight gain.[1,28]

Acquired hypothalamic obesity is not a lifestyle problem. It is a neuroendocrine disease and recognising that is essential for managing it appropriately and supporting patients and families effectively.[1,10,28]

Q: Why is expanding awareness of acquired hypothalamic obesity critical for improving patient outcomes?

Expanding awareness is fundamentally about understanding the problem and intervening early.[1,10] When clinicians understand acquired hypothalamic obesity, they are better able to recognise it, contextualise accelerated weight gain, and identify it at an earlier stage.[1,10]

Awareness helps with early detection and early intervention.[1,10] The earlier clinicians recognise acquired hypothalamic obesity, the greater the opportunity to initiate interventions that may help limit weight gain. Once significant weight gain has occurred, it becomes much more difficult to manage.[1,10,18,28]

Understanding the disease also allows clinicians to counsel patients and families more effectively. If families know what to look out for, they are more likely to report clinical features early, which supports earlier identification and management.[1,10,18,28]

Ultimately, improving awareness increases the likelihood that acquired hypothalamic obesity is recognised promptly, managed appropriately, and supported in a way that helps preserve quality of life for patients and families.[1,10,18,28]

Summary and key takeaways

Acquired hypothalamic obesity 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.[1,2,10] As noted by Professor Paul Dimitri, it is pathophysiologically distinct from general obesity and is driven by hyperphagia and reduced energy expenditure.[10,19]

Accelerated and sustained increases in BMI should prompt consideration of acquired hypothalamic obesity, particularly in at-risk populations.[9,10] The onset is variable, with weight gain occurring anywhere from weeks to 3 years following hypothalamic damage.[1,11–14]

Conventional lifestyle interventions are largely ineffective due to the underlying pathophysiology of the disease.[28] Acquired hypothalamic obesity places a substantial physical, psychological, and social burden on patients and caregivers, underscoring the need for timely recognition and support.[10,18,28,33]

Optimising outcomes requires access to coordinated multidisciplinary care, alongside the implementation of routine monitoring protocols to enable earlier identification and intervention.[10] Improving awareness across specialties remains critical to addressing current gaps in care.

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