Hypothalamic syndrome

Hermann L. Müller[1†], Maithé Tauber[2,3], Elizabeth A. Lawson[4], Jale Özyurt[5,6], Brigitte Bison[7], Juan-Pedro Martinez-Barbera[8], Stephanie Puget[9,10], Thomas E. Merchant[11] and Hanneke M. van Santen[12,13]

[1] Department of Pediatrics and Pediatric Hematology/Oncology, University Children's Hospital, Klinikum Oldenburg AöR, Carl von Ossietzky University, Oldenburg, Germany

[2] Centre de Référence du Syndrome de Prader-Willi et autres syndromes avec troubles du comportment alimentaire, Hôpital des Enfants, CHU-Toulouse, France

[3] Institute Toulousain des Maladies Infectieuses et Inflammatoires (Infinity) INSERM UMR1291 - CNRS UMR5051 - Université Toulouse III, France

[4] Neuroendocrine Unit, Massachusetts General Hospital, and Department of Medicine, Harvard Medical School, Boston, MA, USA

[5] Biological Psychology Laboratory, Department of Psychology, School of Medicine and Health Sciences, Carl von Ossietzky University, Oldenburg, Germany

[6] Research Center Neurosensory Science, Carl von Ossietzky University, Oldenburg, Germany

[7] Department of Neuroradiology, University Hospital Augsburg, Augsburg, Germany

[8] Developmental Biology and Cancer Programme, Birth Defects Research Centre, UCL Great Ormond Street Institute of Child Health, University College London, London, UK

[9] Service de Neurochirurgie, Hôpital Necker-Enfants Malades, Sorbonne Paris Cité, Paris, France

[10] Service de Neurochirurgie, Hopital Pierre Zobda Quitman, Martinique, France

[11] Department of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

[12] Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, University Medical Center, Utrecht, the Netherlands

[13] Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

†**email:** mueller.hermann@klinikum-oldenburg.de

Author contributions

Introduction (H.L.M. and H.M.v.S.); Epidemiology (H.L.M.); Mechanisms/pathophysiology (E.A.L. and J.-P.M.-B.); Diagnosis, screening and prevention (H.L.M., M.T., E.A.L. and B.B.); Management (H.L.M., M.T., E.A.L., J.Ö., S.P., T.E.M. and H.M.v.S.); Quality of life (H.L.M., M.T., E.A.L., J.Ö. and H.M.v.S.); Outlook (H.L.M. and H.M.v.S.): Overview of Primer (H.L.M.).

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Abstract

Hypothalamic syndrome (HS) is a rare disorder caused by disease- and/or treatment-related injury to the hypothalamus, most commonly associated with rare, non-cancerous parasellar masses, such as craniopharyngiomas, germ cell tumours, gliomas, cysts of Rathke's pouch and Langerhans cell histiocytosis, as well as with genetic neurodevelopmental syndromes, such as Prader–Willi syndrome and septo-optic dysplasia. HS syndrome is characterized by intractable weight gain associated with severe morbid obesity, multiple endocrine abnormalities and memory impairment, attention deficit, reduced impulse control as well as increased risk of cardiovascular and metabolic disorders. Currently, there is no cure for this condition but treatments for general obesity are often used in patients with HS, including surgery, medication and counselling. However, these are mostly ineffective and no medications that are specifically approved for HS are available. Specific challenges in HS are due to the fact that the syndrome represents an adverse effect of different diseases, and that diagnostic criteria, aetiology, pathogenesis and management of HS are not completely defined.

[H1] Introduction

Hypothalamic syndrome (HS) is a condition that results from damage to the hypothalamus, which can be caused by diseases or their treatment. Neoplastic diseases such as craniopharyngioma (a histologically low grade tumour of the intrasellar or suprasellar region) are the most frequent cause of HS. Although most sellar masses are of low-grade histological presentation and most individuals with intrasellar or suprasellar tumours have excellent prognosis in terms of overall survival[1], survivors may experience devastating consequences from hypothalamic damage that leads to HS[2-10]. Besides neoplastic diseases, several genetic disorders, such as Prader–Willi syndrome (PWS)[11], or developmental malformations, such as septo-optic dysplasia (SOD)[12], and, in rare cases, traumatic brain injury are also associated with hypothalamic sequelae. PWS is an imprinting disorder that is caused by loss of expression of paternally inherited genes from chromosome 15 (q11–13 region) and characterized by impaired function and development of the hypothalamus[13]. The hypothalamic–pituitary axis is a central coordinator of growth, reproduction and homeostasis (Figure 1); it maintains homeostasis by regulating physiological functions, such as heart rate, blood pressure, temperature, thirst, electrolyte balance, appetite, energy metabolism and sleep, via complex integration of feedback systems and hormone secretion. In addition, the hypothalamic–pituitary axis is crucial for modulating the emergency response to stress via the adrenal gland (or the hypothalamic–pituitary–adrenal, axis). Accordingly, disease and/or treatment-related damage to the hypothalamus leads to disturbed hunger–satiety and thirst sensations, decreased energy expenditure, behavioural problems, circadian rhythm disruption, temperature dysregulation and pituitary deficiencies[14,15]. Patients with HS are at great risk of developing metabolic syndrome (defined as the presence of obesity, dyslipidaemia, hypertension and altered glucose metabolism) and comorbidities leading to premature mortality. The high prevalence of weight gain or obesity among individuals with HS has led to the establishment of a clinical diagnosis of 'hypothalamic obesity syndrome', particularly in the USA[16]. However, in this Primer, we consider 'hypothalamic syndrome' as not being limited to presentation with obesity but also encompasses frequently encountered clinical manifestations of HS such as memory deficits, temperature dysregulation, neuropsychological dysfunction, eating disorders, dysbalance [Au:imbalance?] of circadian rhythms, and several neuroendocrine and pituitary deficiencies. No specific treatments exist for HS, so management usually focuses on addressing the symptoms of the

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condition, most commonly obesity, using standard therapeutic approaches such as pharmacological agents (central stimulating agents, GLP1R agonists, and others), bariatric, neuropsychological and rehabilitative interventions.

This Primer reviews the most important symptoms of HS and the different underlying diseases that cause it, risk factors for the syndrome and current therapeutic interventions to address the sequelae of hypothalamic dysfunction. Some very rare conditions or events with potential risk for HS, such as severe traumatic brain injury, are mentioned but not discussed further. Furthermore, novel aspects and perspectives for future research are discussed.

[H1] Epidemiology

The epidemiology of HS is not well known because incidence and prevalence are related to very rare underlying diseases, including craniopharyngiomas, cysts of Rathke's pouch, germ cell tumours (GCTs), optic pathway gliomas (OPGs) and Langerhans cell histiocytosis (LCH). Craniopharyngiomas account for 2–5% of all brain tumours and 5.6–15.0% of paediatric intracranial tumours[17]. Craniopharyngioma is diagnosed with two peaks of incidence: one peak in 10–19 year old individuals (29%) and a second peak in adults 30–49 years of age (25%). Prevalence does not differ between the sexes (male/female ratio is 0.95) [18]. Global variations in incidence and outcome after craniopharyngioma are difficult to assess as studies from low- and middle-income countries are lacking. For example, an epidemiological study from Egypt[19] mainly reported on surgical approaches and outcomes, whereas a Chinese study[20] focused on the clinical manifestations of craniopharyngioma without specific information on comorbidities. A high postsurgical mortality rate (32%) has been reported in a Nigerian study[21], although mortality was lower in studies from Turkey (7%)[22] and Egypt (6%)[19]. In a review of cases in Jordan[23], 5-year overall survival was 87±7%, which is similar to that in high-income countries (**Table 1**).

The incidence of cysts of Rathke's pouch is unclear, but these growths are estimated to account for 0.5–3.5% of all intrasellar lesions in children and adults[24]. The incidence of intracranial GCTs differs among various ethnic groups[25]. GCTs account for 8–15% of all paediatric central nervous system (CNS) tumours in Japan, Taiwan and Korea, compared with only 0.1–3.0% of those in Europe and North America[26-30]. In addition to variation in patient definitions and tumour classifications in these studies, genetic predisposition

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in Asian populations potentially explains this difference[28,29].

OPGs, which are diagnosed as isolated sporadic lesions or as part of neurofibromatosis type 1 (NF1), comprise 2–5% of paediatric intracranial tumours and have an overall annual incidence of 3–4 cases per 100,000 population in the United States[31]. The Surveillance, Epidemiology, and End Results (SEER) Program found that: that OPG prevalence is higher in white children (67%) than in Latino (17%), African-American (7%) or Asian (5%) children in the USA[31,32].

The annual incidence of LCH in children is 4.6 cases per million population, which decreases substantially with increasing age[33,34,35]. **[Au: Please clarify in which populations. Worldwide?]**By contrast, overall incidence of LCH was higher in a Swedish paediatric population (8 cases per million population per year)[36] but lower in British children (2.6 cases per million child years)[37]. LCH occurs more frequently in males than females (male/female ratio 1.2–1.5) and in young children than in adults (median age at LCH diagnosis 3.8–5.9 years)[34,36]. In Greek adults, a lower annual LCH incidence (1.58 cases per million population) has been reported[38].

Prevalence of PWS ranges between 3.3 and 10.0 cases per 100,000 population in Europe[39] and Australia[40]. A 2020 French study[39] observed a PWS incidence of 1 in 21,000 births[41], **[Au: You've included ref. 41 here but retained ref.39. Is this correct?]** whereas previous studies from Australia[42] and Belgium[43] reported a lower incidence (~1 in 27,000 births) and an Australian study[44] observed an incidence of 1 in 15,830 births. The incidence of SOD is 10.9–50.0 cases per 100,000 population per year in Northwest England and Northern Canada[45,46].

[H1] Mechanisms/pathophysiology

[H2] The healthy hypothalamus

The neurons and glial cells in the hypothalamus are mostly grouped in nuclei, which control specific neuroendocrine and autonomic functions. These nuclei are duplicated and located on both sides of the 3rd ventricle. The hypothalamus occupies a small portion of the human brain, only 4ml in a total brain volume of ~1.1–1.2 litres[47,48]. The neuroendocrine function of the hypothalamus relies on the control of the pituitary gland through the secretion of various stimulating and inhibiting hypothalamic factors[49].

The hypothalamus communicates with multiple organs, receiving inputs from the gastrointestinal tract, liver, adipose tissue and pancreatic islet β-cells and sending messages to these organs as well as to the muscles. Neurons in the hypothalamus project to other areas of the brain involved in the autonomic nervous system to control functions such as appetite, metabolic rate, circadian rhythms, thermoregulation, heart rate, blood pressure and locomotion[50,51] (Figure 2). In addition, connections to the limbic system mediate behavioural patterns such as reward, motivation to eat and aggression[52,53]. In this way, the hypothalamus plays a major role in regulating body composition by balancing food intake and energy expenditure.

[H3] Neuroendocrine function. The anterior pituitary gland receives inputs from the hypothalamus in the form of the hypothalamic releasing hormones growth hormone-releasing hormone (GHRH), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH) and gonadotropin-releasing hormone (GnRH), secretion of which may be hampered in case of hypothalamic injury. After stimulation by these hormones, the pituitary releases growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the peripheral endocrine glands. The hormones produced by these peripheral endocrine glands are necessary for cell metabolism, brain development in the young, linear growth, sexual development and bone and muscle strength. Growth hormone, thyroid hormones and male sex steroids directly influence metabolic rate. Deficiencies of these hormones may result in decreased protein synthesis, lipolysis rate, transport of amino acids into cells, and decreased transcription or translation by cells, as well as increased glucose uptake into cells[54], all of which lead to severe neuroendocrine dysfunction and weight gain or obesity. Deficiency of posterior pituitary hormone vasopressin may lead to diabetes insipidus, which is characterized by excessive thirst and polyuria and treated with vasopressin replacement. Recent studies have uncovered a possible oxytocin deficient state, however there is currently no diagnostic test available.

[H3] Autonomic nervous system functions: appetite. The ventromedial nucleus of the hypothalamus (VMH) and the arcuate nucleus are essential for integrating satiety signals (**FIG. 1**). Anatomical and/or functional deficits in these nuclei lead to an imbalance in appetite-regulating hormones in patients with

hypothalamic syndrome, and result in hyperleptinaemia by reduced sympathetic tone, and flattened responses of peptide-yy (PYY) and ghrelin after meals, caused by dysregulation of the autonomic system[55]. The satiety hormone (incretin) glucagon-like peptide 1(GLP1) enhances perception of satiety through binding to its receptors in the hypothalamus and hindbrain. The neurohormone oxytocin, which may be deficient in HS, is anorexigenic, decreasing food consumption, particularly of more palatable sweet and fat-enriched foods, in animals and humans[56]. The effects of oxytocin on eating behaviours likely involve modulation of both homeostatic and reward-related food motivation brain circuitry[56]. Studies in overweight and obese men demonstrate that oxytocin increases functional MRI (fMRI) activation of neural circuitry involved in impulse control in response to images of foods and reduces impulsive behaviour, as assessed by a validated computerized behavioural task[57,58], suggesting that oxytocin may reduce food intake partly by increasing self-control.

[H3] Autonomic nervous system functions: metabolic rate. Due to decreased sympathetic activity, overall metabolic activity is reduced in children with hypothalamic damage. Paediatric patients with craniopharyngioma or PWS have decreased resting energy expenditures (REE) compared with children with multifactorial obesity, which does not seem to result from differences in body composition[59]. However, individuals with PWS harbour a higher fat mass than in simple obesity, under the same degree of BMI, both in children and in adults. In this context, decreased muscle mass is responsible for reduced REE in PWS, but a normal relationship between fat-free mass and REE is maintained in these individuals[60]. Aside from decreased sympathetic activity[61], REE may also be reduced by other factors, such as decreased thyroid hormones, decreased oxytocin signalling, and reduced muscle mass. Energy expenditure itself may be low owing to decreased physical activity caused by initiative loss and depression, daytime somnolence, vision loss, neurological deficits or obesity[61].

[H3] Autonomic nervous system functions: circadian rhythms and sleep. Sleep is a complex neurophysiological process that is regulated mainly in the suprachiasmatic nuclei, which control circadian rhythm. Aside from the suprachiasmatic nuclei, sleep is also regulated by the ventrolateral preoptic nucleus (VLPO) and the lateral hypothalamus area (LHA), which are sleep-promoting, as well as the monoaminergic cell groups (MCGs) that comprise the arousal system. In addition, melatonin, which is secreted by the pineal gland, has an important role in regulating sleep; children with craniopharyngioma

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have altered melatonin secretion and responses to melatonin[62-64]. Secretion of hypocretin (a neuropeptide that regulates various of behavioural and physiological processes) is also impaired in children with PWS and might explain their sleep problems, including hypersomnia and narcolepsy with or without cataplexy. Children with morbid obesity are at risk of obstructive sleep apnea syndrome (OSAS), which is accompanied by snoring, hypoxia and daytime somnolence. The importance of specialized sleep investigations in children with a suprasellar tumour has been reported[65]. **[Au: Please move this sentence seems to the appropriate place of the diagnosis and/or management sections.]**

[H2] Parasympathetic nervous system

Upregulation of the parasympathetic nervous system in children with hypothalamic injury is caused by disinhibition of the parasympathetic signalling. This increased parasympathetic nervous system tone results in increased vagal nerve stimulation of the pancreas, which results in hyperinsulinaemia, especially. This idea is supported by the finding that supradiaphragmatic vagotomy blunts acute hyperinsulinaemia in rats with lesions in the VMH[3,66]. This hyperinsulinaemia occurs mainly in response to glucose and causes increased calorie storage within adipocytes and thus leads to body fat accumulation. In addition, in subjects with obesity low-grade inflammation may be present in peripheral tissues but this has also been shown to occur in the hypothalamus, through which signals of leptin and insulin signalling are impaired. The extent and severity of hypothalamic lesioning is directly related to insulin resistance, regardless of BMI[67,68]. Oxytocin and arginine vasopressin (AVP) are also involved in parasympathetic/sympathetic regulation [69].

[H3] Limbic system function: behaviour, reward and affect. Hypothalamic lesions are frequently associated with specific changes in mind and behaviour, which have been documented in a wide series of human case studies in the past two centuries and in more recent group studies. These neurobehavioural and psychiatric abnormalities comprise cognitive, emotional control and social functioning deficits, mood disorders, and apathy[70,71]. They may arise from disease-induced damage to the hypothalamus, hypothalamic connections with other brain regions, or neighboring brain regions. Secondary brain lesions resulting from surgery, cranial radiotherapy or complications such as hydrocephalus might also contribute to adverse outcomes. However, outcomes are highly variable and depend, to a large extent, on the type and spatial pattern of hypothalamic damage and possible damage to other brain areas. In a systematic

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review that included studies involving children with a craniopharyngioma diagnosis, neurobehavioural (including psychiatric) abnormalities were present in 57% of survivors[72].

The most frequent cognitive deficits associated with hypothalamic damage are anterograde episodic memory deficits; they range in severity from a mild inability to learn, maintain and later recall new information exceeding short-term memory capacity, to now rare cases of severe Korsakoff-like deficits characterized by severe anterograde amnesia, confabulations and disorientation to time and place[70]. In contrast, short-term and working memory, declarative or recognition memory are less severely affected in many cases [73]. If detailed information on lesion locations is provided, episodic memory deficits can be seen to be usually associated with damage to the mammillary bodies in the posterior part of the hypothalamus, which constitute an essential part of the hippocampus-centered limbic network [70,74] (**FIG. 2a**). Deficits in attention, processing speed and executive functions also occur and are likely caused by additional damage to frontal lobe areas[73,75,76]. With the exception of patients with PWS (who generally present with mild or moderate cognitive deficit), intelligence is mostly in the normal range in individuals with HS, but the specific cognitive deficits together with fatigability bear a considerable risk for decreased academic and vocational achievements and health-related QOL[73,77-79].

The hypothalamus is also an integral part of the amygdala-centered limbic system, which is fundamental for mood, affect and emotional processing (**FIG. 2b**). It is well established that damage to this network or abnormal activity of the hypothalamic–pituitary–adrenal axis are related to psychiatric conditions such as mood and anxiety disorders[70,80]. Hypothalamic lesions have also been associated with emotion control deficits, which are indicative of fronto-limbic dysfunctions, such as emotional outbursts, emotional lability, episodic rage, aggressive behaviour and reduced frustration threshold[70,71,81,82]. In a systematic review, 40% of paediatric craniopharyngioma survivors suffered from abnormalities such as depression, anxiety, irritability, emotional outburst or mood swings[72]. Abnormalities in social interactions might similarly be associated with adverse changes to the amygdala-centered limbic system, which largely overlaps with the so-called 'social brain'. Another possible cause for these abnormalities are lesion-induced changes in the release and binding of oxytocin to its receptor in the central nervous system[70,83].

[Au: is this what you meant by release and central receptor binding of oxytocin?]

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From a functional perspective, the hypothalamus controls and activates a number of behaviours that are essential for survival needs and is involved in brain networks that support reinforcement learning and motivated behaviour [84,85]. Consequently, damage to the hypothalamus and associated networks might be related to apathy (a loss of motivation to self-initiate goal-directed behaviours), which has been reported in many case studies and in a study on a group of patients with childhood-onset craniopharyngioma[70,86,87]. Damage to the hypothalamic–pituitary system may result in deficient signalling of oxytocin, which is produced in the supraoptic nucleus (SON) and the paraventricular nucleus (PVN) of the hypothalamus and released directly into the brain and into the systemic circulation via the posterior pituitary gland. Although oxytocin is most well-known for its actions around childbirth (that is, induction of uterine contractions and lactation), oxytocin also has important psychological and behavioural effects in both sexes, including reduction of impulsivity, attenuation of anxiety and depressive symptoms, and improvement in social cognition and behaviours[88,58]. Thus, hypothalamus-derived oxytocin regulates many of the psychological and behavioural processes that are abnormal in HS, and damage to hypothalamic regions involved in oxytocin signalling may contribute to these clinical sequelae.

[H2] Molecular-genetic causes of HS

Structural damage of the nuclei in the hypothalamus owing to congenital abnormalities in hypothalamic development or acquired causes (for example, tumours, surgery, radiotherapy and trauma) and local inflammation, can lead to HS, which manifests in symptoms associated with the specific neuronal population affected by the insult[89]. The mechanisms underlying acquired causes can vary; in the case of severe traumatic brain injury or surgery, the loss of specific hypothalamic neuronal populations will result in HS with various clinical manifestations. Tumours with hypothalamic involvement can cause physical compression and loss of hypothalamic neurons, but evidence also suggests that factors secreted by the tumour cells can also cause neuronal toxicity and cell death, which could lead to HS[90,91]. The three most common causes of HS are sellar and suprasellar masses, [Au: sellar and suprasellar OK?] SOD and PWS.

[H3] Suprasellar masses. Sellar masses (for example, large pituitary tumours with extension into the suprasellar space) can directly damage hypothalamic structures and thereby cause HS. In adults, these tumours are mainly large non-functioning pituitary adenomas, somatotropinomas and prolactinomas[92]. Adamantinomatous craniopharyngioma is the most common pituitary tumour in children and frequently

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invades the hypothalamus[2,93]. With the exception of specific congenital, familial cases, recurrent genetic alterations have not been found for most sporadic pituitary adenomas[94]. By contrast, adamantinomatous craniopharyngioma is caused by the over-activation of the WNT pathway resulting from activating variants in *CTNNB1* that stabilize its gene product β-catenin[95].

In general, the hypothalamic dysfunction in patients with craniopharyngioma is more accentuated than in patients with other pituitary tumours, particularly the resulting pituitary insufficiency, visual impairment and obesity[92]. Adamantinomatous craniopharyngioma is a developmental tumour, and pre-tumoural lesions have been observed before birth in mouse models of adamantinomatous craniopharyngioma [96]. Furthermore, there have been a few cases of prenatal diagnosis of adamantinomatous craniopharyngioma in humans[97]. The presence of tumour cells during embryogenesis could potentially disrupt the development of the hypothalamus, resulting in more severe phenotypes. In addition, adamantinomatous craniopharyngiomas are characterized by the presence of senescent cells, which secrete various growth factors and inflammatory mediators that lead to molecular and cellular changes in surrounding cells[98,99]. Hypothalamic inflammation has been linked to obesity and can cause both cellular damage of relevant neuronal populations and induction of resistance to critical mediators of satiety such as insulin and leptin[100,101].

[H3] Septo-optic dysplasia (SOD). A diagnosis of SOD is made when at least two of the following triad are present: optic nerve underdevelopment; pituitary hormone abnormalities; or midline telencephalic structural brain abnormalities (for example, in the septum, corpus callosum and anterior commissure). Diagnosis is usually made at birth or during childhood, and symptoms may vary greatly in their severity. [102]. SOD can be classified as congenital (owing to genetic variants in various genes involved in brain and pituitary development) or sporadic (caused by environmental factors, such as drug and alcohol abuse during pregnancy), or, in most cases, it can be caused by a combination of genetic variants and environmental factors[103]. Genes mutated in congenital SOD include HESX1, SOX2, SOX3, OTX2, PAX6, BMP4, FGFR1, GLI2, PROKR2, KAL1, ARNT2 and FGF8, which all control specific aspects of the normal development of the hypothalamic–pituitary axis. Of note, no mutations have been found in the vast majority (80–90%) of patients with SOD[103]. The underlying pathogenesis is similar in congenital and sporadic SOD and likely involves developmental defects in anterior neural midline structures during early embryogenesis.

Supporting this notion, fate mapping studies showed that the hypothalamus, septum and eye field map vary closely within the developing anterior neural plate in the early embryo[104]. For instance, the transcription factors *HESX1* and *SOX2*, which are commonly mutated in congenital SOD, are expressed in embryonic neural precursors of the eye, hypothalamus and dorsal telencephalon[105-107]. Similarly, ethanol exposure in early development reduces the expression of genes that are crucial for normal development of the eyes, telencephalon and pituitary gland; for example, *SOX2* and *SHH,*, both of which are mutated in congenital SOD[108-110].

Therefore, the hypothalamic dysfunction observed in patients with SOD (for example, hyperphagia, thermoregulation defects, circadian rhythm alterations and pituitary insufficiency) is of developmental origin.

[H3] Prader–Willi syndrome (PWS). PWS is an imprinting disorder resulting from loss of expression of paternally inherited genes in the q11-13 region of chromosome 15 (ref.[111]). This chromosomal region, which is maternally silenced by imprinting of the maternal allele, includes protein-coding genes and noncoding RNAs[112] belonging to the class of small nucleolar RNAs (snoRNAs) that primarily guide chemical modifications of other RNAs, particularly C/D box snoRNAs (SNORDs).

The minimal chromosomal deletion that is associated with the PWS phenotype, as deduced from individuals with chromosomal translocations, has been confirmed by deleting this region in mice[81]. This deletion removes the *SNORD116* cluster, *SNORD109A* and *IPW*. *SNORD116* and *SNORD109A* are non-coding, small nucleolar RNAs that are involved in modification of other RNAs, while *IPW* is a long non-coding RNA of unknown function. Microdeletions of the *SNORD116* gene cluster have been reported in a few patients with a PWS phenotype, suggesting the crucial role of this gene in the phenotype[113-116]. *SNORD116* is expressed in the hypothalamus and its expression is finely regulated during development. Mice deficient for *Snord116* recapitulate the complete PWS phenotype and its typical trajectory from birth to adulthood, including high lethality, small size, hyperphagia, obesity and reduced energy expenditure [117] Reactivation of *Snord116* in *Snord116*-knockout mice improved survival and growth in a mouse model of PWS[118]. Similarly, deletion of other genes in q11–13 (such as *Magel2* and *Ndn*) in mice result in growth and endocrine defects that are similar to those observed in patients with PWS[119,120].

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Brain abnormalities have been described in patients with PWS, including in cortical regions and the hypothalamus[121]. Study of the transcriptome in patients with PWS showed upregulated genes that signal hunger (overlapping Agouti-related peptide (AgRP) transcriptome) **[Au: I'm not sure what you mean by overlapping AgRP transcriptome? Overlapping with genes activated in response to AgRP? Please clarify.]** , mainly expressed in microglial cells and involved in the inflammatory response, and downregulated genes activated by feeding (pro-opiomelanocortin (POMC) profile), mainly expressed in neurons controlling neurogenesis, neurotransmission and neuroplasticity[122]. **[Au: Edit OK?]** The involvement of the hypothalamus in PWS has been further validated in animal models and post-mortem human samples, which revealed alterations in specific hypothalamic nuclei that control feeding behaviour and metabolic rate, including the infundibular, paraventricular and supra-optic nuclei[123,124].

[H3] ROHHADNET syndrome. Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, and neural tumour (ROHHADNET) is a syndrome that may occur during early childhood and is associated with various forms of hypothalamic dysfunction. Children with the ROHHADNET syndrome may present with rapid weight gain and obesity, growth failure due to GH deficiency, (congenital) hypopituitarism, hypoventilation or neuro-endocrine tumours[125]. Over time, hypothalamic pituitary dysfunction may increase with the development of central diabetes insipidus, which may be difficult to treat due to lack of adequate thirst feeling. **[Au: Edit OK?]** ROHHADNET is very rare, with only ~100 cases published to date[126]. The diagnosis of ROHHADNET syndrome may be challenging but this syndrome should be considered in all children presenting with unexplained rapid onset obesity at a young age. **[Au:OK?]** One of the most severe problems in this syndrome is the hypoventilation in combination with the autonomic dysregulation that can cause cardiorespiratory arrests and death[127]. **[Au:OK?]** No underlying genetic cause has yet been identified. **[Au: Edit OK?]** An immune-mediated pathogenesis has been suggested based on cerebrospinal fluid analysis showing intrathecal synthesis of oligoclonal bands and antihypothalamus and antipituitary antibodies in patients with ROHHADNET. **[Au: Edit OK? Please reference this statement.]** In addition, immunosuppressive treatment (with, for example, cyclophosphamide, rituximab, immunoglobulin and glucocorticoids) was effective in several patients with ROHHADNET syndrome and ganglioneuroblastoma[128,129]. The hypothalamic dysfunction may be severe

in ROHHADNET, requiring intensive monitoring of fluid management, steroid supplementation therapy and strict obesity management. [Au:OK?]

[H1] Diagnosis, screening and prevention

[H2] Symptoms of HS

Children with HS may present with considerable weight gain or obesity, pituitary dysfunction, diabetes insipidus, temperature instability and/or sleeping disorders. In addition, children with hypothalamic damage can have specific behavioural disorders with disrupted impulse control, aggressiveness, and episodic rage, as well as impaired social, emotional and neurocognitive functioning. In children with suprasellar tumours, social abilities can be impaired owing to damage to prefrontal structures during neurosurgery, especially with the subfrontal approach [72].

Many but not all children with hypothalamic damage develop inappropriate feelings of hunger, which, in combination with the above-mentioned impulse disorders, can result in food cravings and overeating. This altered hunger-satiety can be assessed by history-taking or use of a food diary.

Children with hypothalamic damage may also show symptoms of a sleep disturbance, including problems with initiating or maintaining sleep, waking up earlier than desired and increased daytime sleepiness. Sleep problems can be well assessed by history taking. A diagnostic flowchart has been proposed to aid diagnosis of sleep problems in children after treatment for a (supra) sellar brain tumour[65]. [Au: Add the sentence in the Mechanisms section about sleep problem diagnosis and monitoring here?]

In all children presenting with such symptoms and suspicion of HS, brain MRI is indicated to confirm or exclude neoplasms or developmental abnormalities of the suprasellar region. If brain MRI shows no abnormalities, genetic analyses are indicated to evaluate the presence of genetic syndromes such as PWS (**Table 2**). In neonates and in infants the presence of a severe hypotonia with or without sucking deficits is sufficient to prompt DNA testing for PWS. Later on, DNA testing for PWS is indicated in children with early onset of obesity, intellectual disability, behavioural problems, short stature and symptoms of hypogonadism (cryptorchidism in boys) [130]. In case of rapid-onset hypothalamic obesity with no abnormalities on brain MRI and no genetic diagnosis, the rapid-onset obesity with hypoventilation,

hypothalamic, autonomic dysregulation, neuroendocrine tumour (ROHHADNET) syndrome must be excluded[131].

[H2] Grading systems in HS

The presence and severity of HS can be measured using a clinical scale or radiological scale. For children with suprasellar tumours, the well-established Muller radiological score [132,133] has three grades of severity; grade 0: no hypothalamic involvement or lesion; grade I: hypothalamic involvement or lesion of the anterior hypothalamus that does not involve the hypothalamic area of the mammillary bodies and beyond; grade II: hypothalamic involvement or lesion of the anterior and posterior hypothalamic area (that is, involving the mammillary bodies and the area beyond). The severity of radiological damage is, however, not always related to the clinical grade of hypothalamic damage or to the presence of obesity.

To clinically score hypothalamic dysfunction, the following score (adapted from[133-135]) might be used: grade I (mild) if postoperative obesity (BMI> +2.0 standard deviation score (SDS)) is present with no other change in affect or behaviour indicative of hypothalamic damage; grade II (moderate) if obesity or weight gain is present as well as an obvious period of hyperphagia or an associated change in affective behaviour or memory; grade III (severe): if extreme weight gain and severe hyperphagia is present, as well as other clinical manifestations, such as impaired thirst, rage behaviour, or thermoregulation, memory and sleep-wake pattern disturbances. In 10- to 25 year-old RCT-participants with hypothalamic obesity, a MRI scoring systems predicts weight gain as well as response to weight loss therapy. Higher hypothalamic damage, in particular mammillary body damage, was associated with weight loss, after hormonal (glucagon-like peptide receptor agonist) treatment[136]. Attention-deficit problems may also occur owing to damage to limbic structures or the 3rd ventricle. Intellectual ability may be hampered after radiotherapy and is related to the administered dose of radiation therapy and the irradiated volume of the brain[137].

[H2] Identifying underlying causes of HS

[H3] **Imaging characteristics: craniopharyngioma.** Most craniopharyngiomas are loctaed retrochiasmatically and originate within the tuber cinereum, although some originate prechiasmatically in the pituitary gland. Craniopharyngiomas (**FIG. 3a**) vary greatly in size, from small tumours that present as

solid nodules or small cysts, to large-to-giant tumours, primarily with multilobulated cysts, which reach far superiorly in the third ventricle or laterally and posteriorly in the supra- and infratentorial cisterns or the brain parenchyma. Independent of tumour size, imaging characteristics confirm the 90% rule: 90% of tumours are present in a suprasellar location, 90% have cysts, 90% show contrast enhancement of the cyst wall and the solid part, and 90% have calcifications along the cyst wall in an eggshell shape and of the solid part in a popcorn-like pattern. **[Au: Edit OK?]** Cysts can vary in signal intensity on T2- and T1-weighted imaging, depending on protein-concentration of the intracystic fluid or bleeding into the cyst. Surrounding oedema occurs through compression (for example, along the hypothalamo-optic tract), which is not specific and should not be mistaken for infiltration (**FIG. 3d**). The typical aspect of papillary craniopharyngiomas is primarily solid, inhomogeneous with contrast enhancement and exhibiting neither calcifications nor cysts[138,139].

In contrast to other paediatric central nervous system tumours, craniopharyngiomas do not have a spontaneous dissemination in the subarachnoid space. If seeding occurs it is surgery-induced, mainly along the surgical track. Accordingly, a spinal MRI is not needed for initial staging[140].

[H3] Differential diagnosis of other suprasellar tumours leading to HS. Craniopharyngiomas comprise ~50% of tumours in the suprasellar region. Cysts of Rathke's pouch that reach into the suprasellar cistern (not the common intrasellar ones) are rare in comparison to craniopharyngiomas. Cysts of Rathke's pouch show a more homogeneous content than cysts in craniopharyngiomas and are without calcification or nodular enhancement[141].

Optico-hypothalamic glioma is the second most common suprasellar tumour with the potential to cause HS. Because of low cellularity, optico-hypothalamic glioma is bright on T2-weighted imaging without restricted diffusion, and even in large tumours the bright signal in the posterior pituitary lobe tends to persist. These tumours are usually solid and without cysts (**FIG. 3b**).

GCTs are another differential diagnosis. In these tumours, the signal in the posterior pituitary lobe is lost, even in the beginning of the disease, correlating well with the clinical finding of diabetes insipidus neurohormonalis. In contrast to optico-hypothalamic gliomas, GCTs have a high cellularity, intermediate-to-dark signal on T2-weighted imaging and restricted diffusion (**FIG. 3c**).

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Manifestations of LCH can mimic the aspect of suprasellar GCTs with absent posterior pituitary lobe signal, thickened and contrast-enhancing pituitary stalk, and suprasellar location. Prolactinomas are also very rare in the paediatric age group[142]. Pituitary adenomas and sarcoidosis have their hypothalamic manifestations of the disease from the beginning of adolescence and almost never in children[138,139].

PWS is characterized by its typical clinical symptoms **[Au: Add a call out for Box 2?]** with very little imaging change. MRI can detect a reduced volume of the pituitary gland without the typical increase of pituitary gland volume during puberty[143]. Only advanced MRI techniques such as functional MRI and diffusion tensor imaging can demonstrate imaging abnormalities[143]. Functional data indicate that, compared with healthy-weight individuals, patients with PWS show abnormal patterns of neural activity in response to food. These differences are even more accentuated after eating a meal, with hyperactivation of regions of the brain involved in the control of feeding behaviour in patients with PWS[144].

SOD is a visual diagnosis with absent or hypoplastic septum pellucidum, leading to a box-like-aspect of the communicating frontal horns of the side ventricles resulting in an abnormally low position of the fornices and hypoplastic chiasm and/or optic nerves. SOD can be associated with other malformations, including those of cortical development, small pituitary gland, small or absent pituitary stalk and ectopic neurohypophysis (**FIG. 3d**).

[H2] Screening

Screening for signs of HS or of hypothalamic dysfunction should be done in patients at risk, such as those with suprasellar tumours, SOD, PWS or with rapidly developing obesity at young age. For such patients, surveillance of hypothalamic function should be done at specialized centres with experience in hypothalamic disease. Surveillance may be done by monitoring longitudinal growth, BMI, Tanner stage, and pituitary function, including water-salt homeostasis. In addition, other signs of hypothalamic dysfunction must be paid attention to such as sleeping disorders, hyperphagia, behavioural problems, and temperature dysregulation. Prevention of hypothalamic damage in these patients is often not possible, as the hypothalamic damage has already occurred, but prevention of secondary consequences of hypothalamic damage may be attempted by starting early dietary and physiotherapist rehabilitation programs, monitoring

of glucose metabolism, timely supplementation of thyroid, GH and sex steroids for healthy (bone) development and early counselling for behavioural problems.

[H2] Prevention

Prevention of HS in patients with acquired disease such as craniopharyngioma, supra-sellar germinoma or low-grade glioma, can be attempted by further limiting neurosurgical interventions. This may be accomplished by the use of improved imaging techniques, such as 7-Tesla MRI or through task-related functional MRI[145], whereby the hypothalamic structures can be better identified, guiding the neurosurgeon peri-operatively to minimize hypothalamic injury.

[H1] Management

The management of HS during childhood is not a 'one size fits all'-approach[146] but depends on the underlying aetiology of HS, patient age, clinical signs and symptoms and extent of hypothalamic dysfunction[3,13,147,148]. In 4% of patients with childhood-onset craniopharyngioma, a hypothalamic diencephalic syndrome has been observed, resulting in weight loss and cachexia at the time of craniopharyngioma diagnosis, although weight gain during follow up is common finding[149]. Diencephalic syndrome with severe cachexia occurs even more frequently in patients with cerebral low-grade glioma and is associated with high morbidity and mortality[150]. In addition, co-morbidities may be present, such as decreased visual function or behavioural issues. The management of hypothalamic dysfunction might thus differ between patients and change over time.

For children who already have hypothalamic damage at time of diagnosis or develop HS after neurosurgery or radiotherapy, management must focus on correct characterization of the signs and symptoms of hypothalamic dysfunction that are present, which might differ between individuals; a personalized treatment algorithm to achieve these aims has been suggested[3]. In this algorithm, six clinical domains (psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinaemia and hypopituitarism) were identified which could receive therapeutic intervention.

[H2] Psychosocial disorders

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As described above, children with HS may have specific behavioural disorders. For this reason, psychosocial support for patients and their parents is a crucial part of the multidisciplinary team[3]. In all patients with HS, psychosocial assessments are mandatory. Well-validated questionnaires are available that might be used to assess neurobehavioural, social, and emotional dysfunction in patients with craniopharyngioma and might also be applicable to other patients with HS[72]. Identifying the underlying cause for the psychosocial disorder is an important aspect in the treatment of patients with HS, as insights into this disease will help to create the environment in which patients with HS thrive best, which could be achieved using, for example, a predictable day schedule comparable to that needed by patients with acquired brain injury (ABI) [151]. Treatment for a specific psychosocial disorder or psychiatric condition, such as depression, anxiety, impulse-control disorders or severe food craving behaviours requires additional psychosocial and psychiatric support [152] [REF]. In addition to intrinsic factors related to damage to the hypothalamus, individuals affected by "hypothalamic syndrome" and related conditions may be adversely impacted by the psychosocial stressors of chronic disease, among other social ecological factors [153]. Pharmacotherapeutic options, such as dextroamphetamines, may be of additional help to improve hyperactivity and concentration and may be considered to target psychosocial symptoms[154], and methylphenidate may alleviate concentration disorders[155].

[H2] Hyperphagia

Hyperphagia refers to an extreme form of overeating with persistent sensations of hunger and abnormal intake of food relative to the subjects' needs. Methods frequently used to assess hyperphagia include food frequency questionnaires, such as the hyperphagia questionnaire (HQ)[159], as well as food records and 24-hour recall, which all require subjects to record their food intake during a specified period of time. [Au: Edit OK?] These self-reports require compliance, and especially in individuals with obesity, bear a high risk of underreporting food intake[3]. For this reason, observer or caregiver reported assessment instead of self-assessment is strongly recommended, in particular for patients with PWS [156,160].

The observation that not all children with hypothalamic injury develop hyperphagia may reflect the fact that specific nuclei regulate appetite and that, in some, these may still be intact[10]. Management of hyperphagia is achieved by recognition and education, in combination with dietary and psychosocial

counselling. Several drugs have been used in attempts to reduce hyperphagia. Stimulants such as dextroamphetamine, which are also used for attention deficit disorders, might improve hyperphagia by inhibiting re-uptake of dopamine, norepinephrine and/or serotonin. Methylphenidate might evoke a food reward response and suppress the drive to eat and seems to have beneficial effects on hyperphagia and weight development in patients with craniopharyngioma[155]. In five studies assessing the effects of GLP1 agonists on eating behaviour and BMI, improved hyperphagia symptoms and weight loss were reported in most patients with hypothalamic obesity (all adults)[161-165]. Oxytocin-based therapeutics are under investigation as a potential treatment for hyperphagia and obesity in HS. Other drugs that have been considered for hyperphagia include serotonergic agents that influence within-meal satiation and post-meal satiety processes, and overall total food intake, although this intervention was not successful (**Table 3**).

The role of bariatric surgery in HS is still controversial. Patients with craniopharyngioma who have HS presented with a 22%-weight loss at 5-year follow-up after bariatric surgery, independent of the type of bariatric intervention**[166]**. Irreversible bariatric interventions such as Roux-en-Y gastric bypass were observed to be less efficient in weight reduction [166] and are discussed controversially in the pediatric age group due to ethical and legal considerations[167]. In another retrospective multicentre observational study, Roux-en-Y gastric bypass was effective at up to two years of follow up[168], but relapse of obesity occurred and questions about safety issues with pituitary hormone replacement therapy have been raised. Other studies observed no major changes in endocrine hormone replacement after bariatric interventions[166] (see above).

[H2] Sleep disturbances

Sleep problems may greatly impact family life, reduce energy during the day, promote day-time sleepiness, and increase food desire and BMI[169]. Detection of sleep problems and early referral to a specialized sleep clinic may reveal the aetiology of the sleep disturbance and will give direction to the proper treatment[65]. The first step in assessment of the sleep disturbance is taking an extended sleep history, in which special attention is paid to sleep factors, child disease factors, psychological factors, family factors, environmental factors and physical activity[65]. The second step may be to use a sleep questionnaire, suitable for the age. In addition, actigraphy may confirm a disturbed sleep pattern such as prolonged sleep onset, early morning

awakening or taking frequent naps during the day. With this information, the first steps in treatment can be taken to optimize sleep wake rhythm. If sleep symptoms remain, referral to a sleep expert center may be helpful. To exclude obstructive sleep apnea syndrome (OSAS), polysomnography with capnography may be performed. This will also give insight in sleep latency time and sleep structure. A 24h melatonin test may help to differentiate sleep problems as caused by a problem of the circadian rhythm due to disturbed melatonin excretion or a disturbed response to melatonin [63,64,170,171]. Treatment may vary greatly depending on the aetiology, from improving sleep hygiene, coaching for worrying thoughts, anxiety or depression, to night ventilation for obstructive sleep apnea syndrome.

[H2] Decreased energy expenditure

Management of decreased energy expenditure may be aimed at increasing physical exercise by active daily physiotherapy or sports, in combination with adequate treatment of underlying causes such as sleep problems and pituitary insufficiencies. In addition, treatment with dexamphetamines increases resting energy expenditure in patients with hypothalamic damage, positively influencing energy expenditure and feeding behaviour[172]. Treatment with dexamphetamines has resulted in either weight stabilization or reduction in three other small retrospective cohorts[154,173,174] (**Table 3**). Oxytocin administration in animal models of obesity results in weight loss that is, in part, due to an increase in energy expenditure[175], however, human studies have not yet examined effects of chronic oxytocin on energy expenditure. Larger clinical trials will be important to establish the safety, efficacy and underlying mechanisms of oxytocin for weight loss.

[H2] Hyperinsulinaemia

The cornerstone of hyperinsulinaemia management is lifestyle intervention with diet and physical exercise. In addition, medical therapy may be important (**Table 3**). The thiazide diazoxide (a potassium channel activator) and the somatostatin analogue octreotide inhibit insulin release and both decrease insulin concentrations in patients with craniopharyngioma[177,178]. Treatment with the somatostatin analogue octreotide resulted in weight loss and reduction in insulin secretion[179]. However, octreotide was also

associated with clinical relevant gastrointestinal side effects such as gallstone formation[178]. The combination of diazoxide and metformin reduced weight and impaired glucose tolerance[180].

As the gut–hypothalamic feedback loop still seems to work in some patients with hypothalamic obesity[55,181], treatment with the satiety and gut-hormone GLP1 may be considered. GLP1 promotes decreased food intake and binds to receptors in the hypothalamus (arcuate and dorsomedial nuclei), the vagus nerve and the hindbrain, as well the hippocampus and mesolimbic reward pathways. Treatment with a GLP1 agonist (exenatide once-weekly) for 36 weeks resulted in stabilization or reduction of obesity in patients with hypothalamic obesity[157], although this treatment was less effective in another study[182]. Treatment for hyperinsulinaemia is also not one-size-fits-all but must be tailored because the response to GLP1, defined as reduction in adiposity, is greater in patients with greater hypothalamic damage, as determined by MRI[136]. Alternatively, metformin, which is known to increase insulin sensitivity, reduces food intake by decreasing the secretory activity of neuropeptide Y (NPY)- and Agouti-related peptide (AgRP)-expressing neurons in the hypothalamus [180]. No studies have reported beneficial effects of metformin on BMI, although decreased homeostatic model assessment for insulin resistance (HOMA-IR) was observed (**Table 3**). Oxytocin might have beneficial effects on glucose homeostasis independent of weight effects, owing to increased insulin secretion and insulin sensitivity[56].

[H2] Hypopituitarism

In the case of ACTH deficiency, replacement therapy with hydrocortisone is mandatory. However, hydrocortisone over-replacement might negatively affect BMI and body composition. In patients with craniopharyngioma, 11β-hydroxysteroid dehydrogenase type 1 activity, which increases the conversion of cortisone to cortisol, might be upregulated, implying that lower levels of glucocorticoid replacement therapy may be sufficient for these patients[183]. Lowering the hydrocortisone dose in these patients may thus be beneficial for BMI but needs to be balanced with the risk of hypoglycaemia, adrenal crisis and lack of energy.

GH substitution is safe with regard to risk of tumor progression and relapse in craniopharyngioma and other tumour types. Growth can be improved by GH, whereas the development of obesity is not influenced by GH substitution. However, early initiation of GH substitution after craniopharyngioma diagnosis might

have beneficial effects on weight development and neuropsychological outcome [54]. Levothyroxine should be substituted in a dose sufficient to achieve free T4 levels in the mid-to-upper half of the reference range in order to support weight stabilization [184]. Based on its site of production, oxytocin deficiency is likely in some patients with HS, particularly those with diabetes insipidus (deficiency of vasopressin, a hormone produced and stored in close proximity to oxytocin stores in the posterior pituitary). Low levels of basal and/or stimulated salivary oxytocin have been measured in patients with craniopharyngioma[83,185-187] or hypopituitarism (with or without diabetes insipidus) compared with healthy controls and are linked to clinical endpoints, such as anxiety[188] and worse social cognition[189,190]. Furthermore, low levels of fasting serum oxytocin were observed in men with diabetes insipidus compared with healthy controls with no pituitary disease or men with similar anterior pituitary insufficiencies and hormone replacement; all groups were matched for BMI and age[191]. In addition, men with diabetes insipidus but not those with similar anterior pituitary deficiencies without diabetes insipidus had higher levels of anxiety and depression, and worse social emotional functioning, than healthy controls. The number of oxytocin neurons is deficient in patients with PWS on autopsy[192]. Together these data suggest that decreased oxytocin signalling could contribute to clinical manifestations of HS and raise the question of whether oxytocin-based therapeutics could be useful in treating these patients.

[H2] Neurosurgical aspects in HS

The surgical resection of tumours with close connection to hypothalamic areas is challenging. The type of surgery (ranging from biopsy to a gross total resection) must be integrated in a global multidisciplinary strategy based on the type of tumour. The surgeon's goal, regardless of the procedure, is always to avoid additional damage to hypothalamic structures. To that end, in case of hypothalamus involvement, a subtotal resection should be done to preserve hypothalamic structures as much as possible, as, for example, in craniopharyngioma grade 2[2,15,132,133,193,194]. Indeed, hypothalamic involvement, especially in children but also in adults, increases the likelihood of postoperative obesity and HS, and surgical damage to the hypothalamus is associated with increased risk of HS[2,133,193,195-197].

For craniopharyngioma, a grading system for hypothalamic invasion on preoperative MRI (which is related to postoperative risk of HS), has been proposed to help guide surgeons in choosing the best surgical

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approach to spare the hypothalamus[132,133,195]. These classifications showed predictive value for outcome after surgical resection[194,198-200]. In the KRANIOPHARYNGEOM 2000 study ($n = 120$), surgical lesions of the anterior and posterior hypothalamic areas were associated with higher increase in BMI SDS 36 months after diagnosis (increase in BMI SDS: +3.22 SDS) compared with patients without a hypothalamic lesion (increase in BMI SDS: +0.45 SDS) or only an anterior lesion (increase in BMI SDS: +0.74 SDS) [132]. Complete neurosurgical resection increases the risk of developing HS[201]. For this reason, further hypothalamic damage might be prevented by limiting surgical interventions and using new radiotherapy techniques such as proton beam radiotherapy[193,202].

Similar to craniopharyngioma, a risk-adapted surgical strategy should be applied for other lesions involving the hypothalamus and should take into account the preoperative clinical signs (including predominant side of visual impairment, signs of raised intracranial pressure, signs of hypothalamus involvement (such as overweight), diencephalic syndrome [149], behaviour troubles, and endocrine status) and also a careful examination of the preoperative MRI. A still limited knowledge of this anatomical region that is rich in functional structures, as well as identification of their possible displacement or distorsion[203-205] or invasion by the tumour, are essential to assemble the appropriate strategy and choose the best treatment modality. A high-resolution segmented MRI hypothalamic atlas[206] is helping to guide surgery but its clinical application to large lesions involving or displacing the hypothalamus remains to be demonstrated.

In most patients with HS, it is often necessary to determine a therapeutic strategy that includes a tailored surgical approach (for example, staged or not) for each case. Furthermore, the on-site available technologies and surgical expertise might vary considerably between centres, so all these parameters should be taken into account when managing a patient with a lesion affecting the hypothalamus region.

A risk-adapted treatment with a grading system of hypothalamus involvement by craniopharyngioma has been described previously[2]. The same approach can be used for other tumour types developed in this brain region. With regard to surgical interventions in patients with HS, the presented treatment paradigm recommends a surgical strategy focussed on the preservation of hypothalamic and optical functionality.

[H2] Radiooncological aspects in HS

All treatments deployed for (para)sellar tumours, and especially craniopharyngiomas, have risks and benefits. Academic institutions are moving towards improved patient selection for surgery and radiotherapy[207]. Both treatment approaches result in similar rates of overall survival[208], but the rate of tumour progression after radical surgery is generally higher than that observed after radiotherapy, and those patients who experience tumour progression after surgery may receive radiotherapy with no impact on overall survival[209]. The acute and long-term effects of surgery and radiotherapy have also been compared[210]. The troubling acute effects of radical surgery include diabetes insipidus, vision loss, stroke and, rarely, peri-operative death; the long-term effects are not well-documented but include reduced performance status and neurocognitive impairment affecting specific domains and QOL[211]. The acute effects of irradiation are self-limiting and include nausea, emesis, profound fatigue and temporary hair loss corresponding to the treatment portals. The long-term effects are of greater concern and include vasculopathy, necrosis and secondary tumours, both benign and malignant. Both surgery and radiotherapy are associated with panhypopituitarism and metabolic syndrome and might contribute differentially to fatigue[7], narcolepsy[62-64,212] and hypothalamic obesity[3]. However, there is a consensus that radical surgical strategies result in more severe HS than radiotherapy and that radiotherapy is not associated with the development of diabetes insipidus[213,214].

Conformal radiotherapy was developed several decades ago to escalate the radiation dose safely and improve local control in tumours that are difficult to treat. This approach has been applied to treat childhood craniopharyngioma and to reduce the adverse effects of radiotherapy. Clinical trials were designed to test the ability of conformal radiotherapy to reduce the targeted volume and the potential for adverse effects in children with craniopharyngioma without compromising patient safety. Preliminary results demonstrate a high rate of local tumour control and the importance of tumour imaging during treatment[215]. The advantages of limiting the prescribed dose to the tumour and sparing normal tissue from exposure provided the rationale for using proton therapy, which promises even greater sparing of normal tissue[214,216].

As craniopharyngioma is a rare paediatric brain tumour, the number of radiotherapy patients represented in single-institution reports is inevitably limited. The large proportion of patients initially treated with surgery and subsequently with irradiation, the high rate of tumour control after radiotherapy, and the need for long-

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term follow up to observe disease control and functional outcomes all have an impact on the ability of investigators to identify prognostic factors associated with radiotherapy.

In contemporary series that included paediatric patients treated with radiotherapy, including proton therapy, excellent 5- and 10-year progression-free and overall survival rates have been reported[217]. In a cohort of more than 100 paediatric patients who were followed for a minimum of 10 years, conformal photon radiotherapy resulted in high rates of progression-free survival ($78.84 \pm 4.10\%$) and overall survival ($96.02 \pm 1.95\%$), and this study highlighted causes of death unrelated to disease progression and severe late complications[218]. The 10-year cumulative incidence of late severe complications, which are often used for patient selection, was low: $1.98 \pm 1.39\%$ for necrosis, $1.99\% \pm 1.40\%$ for any secondary tumour, and $1.00\% \pm 1.00\%$ for a secondary malignant tumour. Although the 10-year cumulative incidence of vasculopathy, as documented by cerebral angiography, was high ($7.93\% \pm 2.71\%$), few patients required revascularization surgery[219].

The need for expert care and experience when planning and delivering radiotherapy has not gone unnoticed by patients, parents and medical caregivers. There is a trend to refer patients to proton therapy centres that have the capacity to perform image-guided pencil-beam scanning proton therapy, the ability to conduct MRI during the treatment course to monitor changes in the size and shape of the targeted volume, and access to the anaesthesia resources that are often required for treating young patients [214]. There is also a trend to couple the normal tissue–sparing properties of proton therapy with less invasive neurosurgery procedures, including catheter and reservoir placement via a burr hole or limited craniotomy, transnasal transsphenoidal decompression, or decompression of the tumour complex without approaching the hypothalamus or the hypothalamic pituitary axis [2]. In rare cases, radiotherapy is applied without surgical intervention, with the diagnosis being established by CT and MRI [220]. In the context of our recommendation of hypothalamus-sparing surgical strategies and consecutively **[Au:consequently?]** higher rates of residual disease, radiotherapy plays an important role in efficient treatment and preventing further exacerbation of HS. **[Au: Edit OK?]**

[H2] Management of PWS

PWS[11] was first described as a syndrome of obesity, short stature and hypogonadism, but is now considered as a severe genetic neurodevelopmental disorder owing to a specific hypothalamic dysfunction, which drives a unique developmental trajectory comprising 3 dimensions — nutrition, endocrine development and neurodevelopment, including dysautonomia[13]. Hyperphagia has a strong impact on family daily life and has been rated as a very important consideration when using the Zarit burden questionnaire[223], as it requires strict control of access to food to prevent life-threatening obesity. One approach is to implement early treatment in a short period of time during the first months of life corresponding to a defined period of development to modify early symptoms comprising sucking deficits and poor interactions and influence the course of the disease. For example, infants with PWS who received a short 7-day course of intranasal oxytocin administration before 6 months of age (either 4 IU every other day or 4 IU daily or 4 IU twice a day) had increased oral and socials skills with long-term good tolerance and motor development[224]. There was no control group in this first publication and a double-blind, placebo-controlled study is ongoing (NCT04283578). Preventive psychotherapy is proposed to help patients and families to implement adaptive strategies. **[Au: Is this your proposal or someone else's? If the former, please make this clear by rewording to We propose preventive psychotherapy…. If the latter, please provide a reference(s).]**

Growth hormone deficiency (owing to a deficit of proconvertase I that leads to decreased maturation of hypothalamic hormones, insulin and ghrelin [225]) occurs in most patients with PWS [226]. Human recombinant growth hormone was the first and is still the only medically approved treatment for children with PWS and is usually started during the first year of life. Many patients display high sensitivity to growth hormone treatment [227]. Growth hormone treatment and early multidisciplinary care have changed the course of the disease [226,229,230]. In phase III clinical, randomized-controlled trials comparing growth hormone treatment to no treatment/placebo in children with PWS, 50% of children receiving growth hormone were lean and young adults were leaner with less comorbidities[231-233]. Long-term safety of growth hormone treatment is now confirmed[234]. In 2021, the International PWS Organisation (IPWSO) applied for authorization of growth hormone treatment in adults to maintain the benefits of the treatment and prevent worsening of obesity and comorbidities including diabetes[235].

All patients with PWS present with hypogonadism, which is more frequently due to gonadal defects than hypothalamic dysfunction[237] and evolve with age. Hypogonadism should be systematically investigated,

with physiological gonadal steroid replacement[238]. Hypothyroidism is observed in more than 50% of patients with PWS, with a typical but not consistent hypothalamic signature of moderately high level of TSH and low free T4 (ref.[240]). Corticotropin deficiency is observed in fewer than 10% of patients with PWS. Precocious hypothalamic–adrenal axis activation that induces premature or precocious adrenarche with advance of bone age, which, by increasing androgens and oestrogens levels, may induce precocious or premature puberty with decreased growth, is observed in 30% of young children with PWS[13]. **[Au: Edit OK?]** Ongoing analysis of a study using aromatase inhibitor treatment to decrease oestrogens production will possibly bring interesting results. **[Au: Please reference this statement. Is this clinical trial identifier NCT01520467?]**

Several randomized placebo-controlled trials of intranasal oxytocin or oxytocin receptor agonists for the treatment of HS in children and adults with PWS have been published. Studies have been small (≤30 individuals) with varying doses (for example, 16–80 IU total daily oxytocin administered in1–3 doses) for up to 3 months and have yielded inconsistent results[241-246]. In three of six studies of intranasal oxytocin, marked improvement in symptoms (for example, emotion regulation, disruptive behaviour, social behaviour and hyperphagia) was demonstrated overall or only in subsets of patients with PWS (for example, younger children, boys, and those with deletions)[241,243,246]. However, three studies reported negative effects (for example, on mood-related symptoms, temper outbursts, repetitive behaviours and hyperphagia) with oxytocin compared with placebo in all participants or only in subsets of patients with PWS (for example, older children or those on higher doses)[243-245]. One potential explanation for negative effects of oxytocin, particularly at higher doses, is crossreactivity vasopressin receptors, as vasopressin has opposing actions to oxytocin on emotional behaviours[88]. Administration of intranasal carbetocin, a longer-acting selective (that is, without action on vasopressin receptors) oxytocin receptor agonist (3 times daily for 2 weeks) reduced hyperphagia in children with PWS[156]. To date, no studies have reported weight loss with intranasal oxytocin or carbetocin in patients with PWS.

Various therapeutic approaches have been developed or are ongoing or planned **[Au:for treatment of obesity in PWS, or for something else? Please clarify.]** (Table 1). **[Au: Should this be table 3?]** In a prospective, randomized crossover trial in 9 children with PWS, the somatostatin analogue octreotide was ineffective in treating weight loss and hyperphagia despite decreasing ghrelin levels[247]. **[Au: Edit OK?]** In

a phase II trial **[Au: specified study design, correct?]** in 13 children with PWS, diazoxide choline controlled-release showed positive effects by reducing hyperphagia and fat mass and increasing lean body mass, although the well-known adverse effects of the drug were observed[248]. A phase III randomized clinical trial with an open label extension (NCT03714373) is ongoing. **[Au: specified trial identifier, correct?]** Metformin was used in 15 children with PWS and had some effects on food-related problems but not on weight loss[249]. **[Au: Edit OK?]**

The methionine aminopeptidase 2 inhibitor beloranib is primarily used in oncology as an angiogenesis inhibitor and has dose-related severe adverse effects. **[Au: Edit OK? added some additional background.]** In a randomized controlled trial 107 adolescents and adults with PWS, lower doses of beloranib gave excellent results in terms of reduction in weight and BMI, although 2 drug-related deaths from pulmonary embolism[249] resulted in development of this drug being discontinued. However, its mechanisms of action seem to be optimal in PWS and other causes of hypothalamic obesity. Since then, drugs that target the ghrelin system, which is impaired in PWS, have been developed[250], although it is important to take into account the developmental phases of the disease because the ghrelin system is differently impaired at different ages[250]. **[Au: Edit OK?]** In a multicentre randomized controlled trial in 47 adolescents and adults with PWS , the synthetic unacylated ghrelin analogue livoletide significantly improved the Hyperphagia Questionnaire (HQ) score and reduced waist circumference, fat mass and postprandial glucose levels compared with placebo, although body weight was unchanged[251]. **[Au: Edit OK?]** In a phase III trial of this analogue (NCT03790865), the primary and secondary endpoints were not met in the initial 12-week core period and so development of the drug was halted. **[Au: Edit OK? Trial identifier correct?]** GLP1 agonists have also been studied: a randomized controlled trial of liraglutide in 56 children and adolescents with PWS was completed in early 2022 (NCT02527200). **[Au: Edit OK? Specified clinical trial identifier, correct?]** In a randomized controlled trial of topiramate treatment in 62 adolescents and adults with PWS, there was a trend towards decreased BMI, dose-dependent improvement in hyperphagia, and dose-related adverse effects, including lethargy and speaking problems[252]. **[Au: Edit OK?]** Other drugs in development **[Au: to treat hypothalamic obesity? Please clarify.]** target endocannabinoids, neurotransmitters and the melanocortin pathways.

Bariatric surgery had been performed as an emergency response to very difficult situations, although experts do not recommend it in PWS as risks **[Au: of complications? Adverse effects? Please specify.]** are higher in PWS than in other diseases of severe obesity and the long-term outcome is **[Au: sometimes? always? Often? Please clarify.]** negative[222,253,254].

[H2] Management of SOD and other causes of HS

Management of HS due to SOD, severe brain injury, inflammation and other rare diseases is primarily focussed on adequate rehabilitation of neurological and ophthalmological deficits and substitution of neuroendocrine, hypothalamic-pituitary deficiencies.

[H1] Quality of life

Quality of life (QOL) of patients with HS can be greatly impaired depending on the extent and severity of hypothalamic dysfunction. **[Au: Is this what you meant by degree?]** QOL may be particularly impacted in patients with diabetes insipidus and inadequate thirst regulation, morbid obesity and behavioural problems, requiring constant monitoring of long-term sequelae. **[Au: monitoring instead of surveillance OK?]**

QOL in relation to HS has been studied extensively in patients with craniopharyngioma, who generally report reduced health-related QOL and impaired psychosocial health[5,7,137,257-261]. Tumour relapse, hypothalamic involvement, repeated surgeries, radiotherapy and the consequences of the tumour or treatment (for example, vision loss, obesity, hypopituitarism, epilepsy and pain) have been shown to reduce QOL of patients with craniopharyngioma[213,261,262]. Patients with craniopharyngioma, especially those with HS, have the worst QOL; in an evaluation of 102 patients with craniopharyngioma, those with no hypothalamic involvement ($n = 60$) self-assessed QOL was higher at baseline ($P = 0.001$) and at follow nup ($P < 0.001$) than for patients with hypothalamic involvement ($n = 42$). In addition, abnormalities in mood, mainly depression and anxiety, have also been reported in patients with craniopharyngioma who have HS[77]. QOL in children with craniopharyngioma may be more affected than in adult patients, partly because paediatric patients more frequently develop HS and do not have the added stress of an established career, professional life and family[263]. The impact that HS has on QOL emphasizes that patients with HS require physical, psychological and psychosocial rehabilitation[264]. QOL have been poorly studied in patients with

PWS and their families. Three studies showed that children with PWS had lower QOL in all dimensions [265-267], with almost 50% considered at high risk for **[Au: reduced?]** QOL[265] compared with children with obesity. Children with PWS rated a higher QOL than their parents (mostly mothers)[266]. **[Au: Added Ref.266, correct?]** More than 50% of the mothers had quit or changed their job after the birth of the child with PWS [266]. Another study reported lower QOL in 15 adults with PWS (mean age 22 years; range 19–42 years)[256]. **[Au: lower compared with which population? Please clarify.]**

[H1] Outlook

Improvement of outcomes in patients with HS must be aimed at preventing or decreasing hypothalamic injury in patients with acquired disease. Reducing the extent and severity of hypothalamic damage will directly improve QOL, morbidity and mortality rates. For patients presenting with acquired or genetic HS, improvement in outcome may be accomplished by personalizing management of hypothalamic damage in centres of expertise, and by future collaborative intervention trials.

Neurosurgery, which can lead to hypothalamic damage and thereby HS, may be limited or rendered unnecessary if systemic therapies were developed. For example, in adamantinomatous craniopharyngioma, increased MAPK/ERK pathway activation [268,269] (owing to genetic variants in CNNB1 and consequent activation of the WNT pathway) was treated with MEK inhibitors, resulting in decreased proliferation and increased apoptosis in mouse and human tumours in vitro[268]. Of note, a single case report showed a significant reduction in tumour size after treatment with a MEK inhibitor in a patient with adamantinomatous craniopharyngioma[270]. Similarly, IL-6 is expressed **[Au: present at high levels? highly expressed? Please clarify.]** in mouse and human adamantinomatous craniopharyngiomas, both in the solid tumour and cystic fluid[268,271,272], and inhibition of IL-6 signalling might potentially be effective against cystic tumours[273]. In papillary craniopharyngioma, the presence of the $BRAF^{V600E}$ mutation provides the possibility of treatment with BRAF inhibitors, and several case reports have observed a successful treatment response[274].

Novel medications for hypothalamic obesity are in development. After careful selection of patients, treatment might be aimed at increasing resting energy expenditure and/or reducing food intake, such as with dextroamphetamines, oxytocin receptor agonists, ghrelin antagonists or GLP1 agonists. Selective

inhibitors of the presynaptic norepinephrine transporter NET, such as atomoxetine, might be used to increase activity of the brown adipose tissue. An even more experimental treatment, brown adipose tissue transplantation, could be used to increase the amount and activation of brown adipose tissue[275].

Randomized placebo-controlled trials of 8-week intranasal carbetocin treatment in children with PWS (NCT 03649477) and 8-week intranasal oxytocin treatment in children and young adults with tumour-induced hypothalamic obesity (NCT 02849743) are ongoing. To date, the data suggest that some but not all individuals with PWS might benefit from interventions to increase oxytocin signalling[156,241-246]. While the safety data thus far are reassuring overall, negative effects of intranasal oxytocin on emotion regulation and behaviour in patients with PWS have been reported[243-245]. Further research is needed to understand whether there are specific subsets of patients with HS who might benefit from oxytocin-based therapeutics and the optimal drug formulation and dosing regimen. Well-powered clinical trials will be important to establish the safety and efficacy of oxytocin-based therapeutics in the treatment of HS.

Tesomet, a combination of the triple monoamine reuptake inhibitor tesofensine and the selective β1 receptor blocker metoprolol, received orphan drug status from the FDA for treatment of hypothalamic obesity. In a small randomized controlled trial including 24 adults with hypothalamic obesity, 24-week treatment with Tesomet reduced body weight and had mild adverse effects [276]. Additional trials are needed to demonstrate its efficacy[276].

Another possible interesting new treatment for hypothalamic obesity is deep brain stimulation, which causes a 'functional' lesion or modules a brain network by high-frequency stimulation. This therapy has been used for treatment of Parkinson's disease, obsessive-compulsive disorder, dystonia and epilepsy, and is also being explored for multifactorial obesity and other eating disorders, such as anorexia nervosa. To date, deep brain stimulation for hypothalamic obesity has been used in 3 studies, with a total of six patients, including five patients with PWS and one who had received treatment for craniopharyngioma. Targets for deep brain stimulation included the LHA and nucleus accumbens. In PWS, deep brain stimulation of the LHA resulted in a 5.8% increase in BMI, whereas deep brain stimulation of the nucleus accumbens -in a patient with craniopharyngioma resulted in an 8.7% decrease in BMI[277-279]. No severe adverse events were reported in these trials.

These new interventions must be considered experimental and only be given in expert centres or networks with expertise [280] in the context of clinical trials with sufficient power. Considering the rareness of HS, such studies must preferably be done in an international collaborative consortium.

In addition, counselling care-givers in the home environment is an important aspect of management. To successfully maintain a new lifestyle with diet and drug adherence, the patient should have close and intensive guidance and monitoring in the home environment by a multi-disciplinary team, counselled by the expert team. It is important that not only the patient but also family members and individuals in the school or work environment are adequately informed about HS to provide the optimal environment for the patient, to enable their development and participation in society. Transition from childhood to adulthood care in patients with HS is challenging, because in this chronic disease patients' neuropsychological characteristics and long-term and close relationship to treating paediatricians impose problems on necessary changes during transition.

Table 1. Epidemiology of suprasellar masses associated with hypothalamic syndrome.

Condition	Incidence range (per 100,000 persons per year)	Estimated prevalence of HS [Au: Edit OK?]	Cohort or region	Refs[a]
Craniopharyngioma	0.05–0.19	50%	Overall	17,281,282,283,284
	0.12–0.21	[Au:50%?]	Paediatric	283,285,286
Germ cell tumour	0.06–0.09	30%	Overall	287
	0.17	[Au:30%?]	Japan	288
Chiasmatic hypothalamic glioma	3.00–4.00	80%	Paediatric	31, 289
Rathke's cleft cyst [Au: Cysts of Rathke's pouch for consistency?]	0.51–3.5% of sellar and parasellar lesions	20%	Overall	24
Langerhans cell histiocytosis	0.46–0.89	20%	Paediatric	33,35,36
Prader-Willi syndrome	3.30–10.00[b]	100%	Overall	39
Septo-optic dysplasia	0.05	20%	Overall	290
ROHHAD-NET syndrome	100 cases reported worldwide	100 %	Overall	126

[a]Only the most recent and relevant of the published epidemiology studies of the conditions associated with hypothalamic syndrome are included in the table. [b]Prevalence.

Table 2. Genetic testing commonly used to diagnose SOD, craniopharyngioma and PWS.

Condition	Common genetic tests; sensitivity		Refs
	First test	**Second test**	
SOD	DNA sequencing (mutations in *HESX1*, *SOX2*, *SOX3* and *OTX2*); <5% of patients with SOD	DNA sequencing (mutations in *PAX6*, *BMP4*, *FGFR1*, *GLI2*, *FGF8*, *PROKR2*, *KAL1*, and *ARNT2*); <2% of patients with SOD	103,291
Craniopharyngioma	DNA sequencing (exon 3 *CTNNB1* mutations); >70% of ACP tumours DNA sequencing (*BRAF*^{V600E} mutations); >90% of PCP tumours **[Au: Edit OK?]**	NA	2
PWS	Methylation-specific PCR or MS-MLPA to detect abnormal imprinting of the Prader–Willi critical region on the parental chromosome 15; >99% of patients with PWS	CGH and SNPs; 80–90% of patients with PWS **[Au: deleted duplicate entry, OK?]** FISH; 65–75% of patients with PWS **[Au:'of patients with PWS' OK?]**	292,293

SOD, septo-optic dysplasia; ACP, adamantinomatous craniopharyngioma; PCP, papillary craniopharyngioma; NA: not applicable; PWS: Prader–Willi syndrome; PCR: polymerase chain reaction; MS-MLPA, methylation-sensitive multiplex ligation-dependent probe amplification; CGH, comparative genomic hybridization microarray; SNPs, single-nucleotide polymorphisms; FISH, Fluorescence in-situ hybridization.

Table 3. Pharmacological treatment approaches for hypothalamic obesity.

Pharmacological agent	Mechanism of action	Patient cohorts (*n*)	Outcomes	Ref
Dextro-amphetamine	Central stimulant, stimulation of noradrenalin, dopamine secretion and dopamine reuptake inhibition	Paediatric CP (5)	Increase in physical activity, reduction of weight gain, stabilization of BMI [Au: Edit OK?]	173
		Paediatric CP (9); paediatric astrocytoma (2); paediatric glioma (1)	Reduction of weight gain and BMI stabilization in 10 of 12 patients, improved daytime sleepiness in 11 of 12 patients	174
		Paediatric CP (3), adult CP (1); paediatric astrocytoma (1); paediatric ganglioglioma (1), paediatric meningitis (1)	Reduction in continuous weight gain and stabilization of BMI	154
Caffeine and ephedrine-HCl	Metamphetamine analogue with sympaticomimetic effect	Paediatric CP (1)	Mean weight loss 13.9%, 6 months after 2.6–5.5 years intervention	294
Mazindol	Sympaticomimetic amine similar to amphetamine	Adult CP (1)	Weight reduction from 70 kg to 60 kg after 3 weeks intervention	295
Methyl-phenidate	Central stimulant, dopamine reuptake inhibition	Paediatric CP (1)	Beneficial against weight gain	155
Octreotide	Somatostatin analogue, reduced beta-cell activation	RCT: paediatric CP (13); paediatric astrocytoma (4); paediatric germinoma (1); paediatric ALL (2)	Reduced insulin secretion, moderate to no improvement in BMI, increased risk of gallstone formation	178
		Paediatric brain tumours (8)	Weight loss and decrease in BMI and insulin secretion after 6 months	179
		Paediatric PWS (9)	Decrease in ghrelin concentrations, no improvement of BMI or appetite, increased risk of gallstone formation	247
Diazoxide	Potassium channel activator, inhibition of insulin secretion	Patients (18) [Au: please complete.]	No BMI change	177
		Paediatric PWS (13)	Reduction in hyperphagia and fat mass, ncrease in lean body mass	248
Diazoxide and metformin	Reduced insulin secretion, reduced hyperglycaemia, improved insulin sensitivity	Paediatric CP (9)	Reduced weight gain, weight loss, peripheral oedema, emesis, elevated hepatic enzymes	180
Metformin	Reduced liver glucose production, improved insulin sensitivity	Paediatric PWS (12)	No weight loss	296
Fenofibrate and metformin	PPARα agonist, improved insulin sensitivity	Paediatric CP (10)	Improved insulin resistance and lipid profiles, no effect on BMI	297
Topiramate	Carbonic anhydrase inhibitor, loss of appetite	RCT: patients with PWS (62)	Trend towards decreased BMI, improvement of eating behaviour	252
Beloranib	Methionine aminopeptidase 2 (MetAP2) inhibitor	RCT: adolescents and adults with PWS (107)	Improvements in hyperphagia-related behaviours and weight loss	249
Exenatide	GLP1R agonist, improved insulin sensitivity, increased satiety feeling, reduced speed of gastric emptying	Adult hypothalamic germ cell tumour (1)	BMI reduction from 37.1 to 29.1 over a period of 2.5 years	163
		Adult hypothalamic tumour (1)	10 kg weight reduction after 16 weeks intervention, stable weight over 4 years	164
		Adult CP diagnosed in childhood (1)	Weight reduction from 88 kg to 77.1 kg after 8 weeks intervention	165
		Paediatric suprasellar tumour (5)	No significant weight loss in total cohort	182
		Adult CP (5), paediatric hamartoma (1), adult astrocytoma (1), adult germinoma (1)	Improved cardiovascular profile; improved metabolic profile; sustained weight reduction	162
		Paediatric CP (4), adult CP (2)	No weight loss in total cohort; stable or decreased weight in responders (60%)	161
		RCT: paediatric suprasellar tumours (42)	Decrease in food intake and total energy expenditure after 36 weeks of exenatide	158

		Paediatric and adults PWS (10)	Decrease in appetite scores and HbA1c but no change in weight, BMI z-score and adiposity [Au: Edit OK?]	[298]
Liraglutide	GLP1R agonists, improved insulin sensitivity, increased satiety feeling, reduced speed of gastric emptying	Adult CP (1)	BMI reduction from 41.8 to 35.3 after 8 months intervention	[162]
Tesomet	Combination of tesofensine (monoamine reuptake inhibitor) and metoprolol	RCT: adult patients with HO (21; 10 with CP) [Au: Edit OK?]	6.3% mean weight loss, mainly due to reduction in fat mass; medication well tolerated	[276]
AZP-531	Analogue of unacylated ghrelin	RCT: adolescents and adults with PWS (17)	Reduction in waist circumference and fat mass but no change of body weight	[251]
Oxytocin	[Au: Please describe the MOA of oxytocin.]	RCT: paediatric PWS (26)	No improvement in hyperphagia; well tolerated	[246]
		RCT: paediatric PWS (23)	No improvement in hyperphagia; well tolerated	[245]
Oxytocin and nal-trexone (opiate antagonist)	Naltroxane decreases appetite and potentiates anorexigenic effects of oxytocin	Paediatric CP (1)	Improvement of hyperphagia and weight loss	[299]
Carbetocin	Intranasal oxytocin analogue	RCT: paediatric PWS (37)	Improvement of hyperphagia and behavioural symptoms; well tolerated	[156]
Substitution with recombinant GH	Beneficial effects of GH on body composition and metabolism	Paediatric CP199	No reduction of BMI during 3 years GH substitution	[300]
		Paediatric CP260	No reduction of BMI during 5 years of GH substitution	[301]
		Paediatric CP47	No BMI reduction with GH during the first 3 years after diagnosis	[302]
		Paediatric CP79	Long-term effect of GH on BMI when substituted during paed and adult age [Au: 'long-term reduction in BMI when GH substituted during childhood and adulthood'?]	[54]

BMI, body mass index; CP, craniopharyngioma; HO, hypothalamic obesity; GH, growth hormone; GLPR1, glucagon-like receptor 1; RCT, randomized controlled trial; METAP2, methionine aminopeptidase 2; PPARα, peroxisome proliferator activated receptor-α; T3, triiodothyronine. Adapted from REF.[2], Springer Nature.

Figure legends

Fig. 1. The human hypothalamus and its nuclei. [Au: 'Anatomy and connectivity of the hypothalamus'?] A schematic of the human hypothalamus depicting the important nuclei and their connections and afferent and efferent hormones. Craniopharyngiomas may arise from epithelial remnants of the craniopharyngeal duct or Rathke's pouch (yellow bar) in infrasellar, sellar, or suprasellar locations. **[Au: Edit OK?]** The hypothalamic nuclei are interconnected through neural pathways; the connection between the arcuate nucleus and paraventricular nucleus (PVN) is highlighted. Hypothalamic-releasing hormones released into efferent blood vessels stimulate the pituitary gland to produce secretion hormones, including thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH)/follicle-stimulating hormone (FSH) and growth hormone (GH). Hunger and satiety hormones (**[Au: including, or such as?]** ghrelin, leptin, insulin and glucagon like peptide 1 (GLP1)) stimulate the so-called orexigenic and anorexigenic responses, respectively, in hypothalamic neurons through afferent blood vessels. **[Au: Edit OK?]** ADH, antidiuretic hormone; **[Au: ADH definition OK?]** AgRP, agouti-related peptide; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; GHRH, growth hormone–releasing hormone; GLP1,; GnRH, gonadotropin-releasing hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, polypeptide-Y; TRH, thyrotropin-releasing hormone. Adapted with permission from Ref. [3], The Endocrine Society.

Fig. 2: Integration of the hypothalamus with the limbic system. The hypothalamus (HYP) is an integral part of two different networks of the limbic system: a hippocampus (HC)-centred network essential for episodic memory (part **a**) and an amygdala (AMY)-centred network relevant for social-emotional functioning (part **b**). Damage to brain regions within these networks or to their connecting fibres contribute to the neurobehavioural and psychiatric abnormalities in hypothalamic syndrome (HS). Episodic memory deficits in HS usually result from lesions to the mammillary bodies (MB) in the posterior part of the hypothalamus or their connecting fibres: fornical fibres projecting from the hippocampus to the MB, or fibres of the mammillo-thalamic tract projecting from the MB to the anterior thalamic nucleus (part **a**). Deficits in social-emotional functioning in HS may result from lesions to hypothalamic nuclei anterior to the MB and, for example, from tumour- or treatment-related damage to other regions of the amygdala-centred network[70] (part **b**). THAL, thalamus; RSC, retrosplenial cortex; VSP, ventral striatopallidum.

Fig. 3. Neuroradiological presentations in hypothalamic syndrome. MRI scans of selected hypothalamic lesions are presented **a** | Typical craniopharyngioma (Müller grade II) with discrete compression and displacement of mammillary bodies and oedema of the right optic tract (arrowhead). **[Au: There is no arrowhead in part a, only two white arrows. please clarify.] b** | Optico-hypothalamic glioma with persistent bright signal of posterior pituitary lobe (arrowhead) and inhomogeneous contrast enhancement. **c** | Mixed germ cell tumour with vanished bright signal of posterior pituitary lobe and contrast enhancement similar to the optico-hypothalamic glioma. **d** | Septo-optic dysplasia with box-like-aspect of the communicating frontal horns (asterisk), low-lying fornices (white arrows), hypoplastic optic nerves (white arrowheads) **[Au: there is only one white arrow and one white arrowhead. Please clarify.]** and closed lip schizencephaly (black arrowheads). **[Au: It's not clear which panels (upper or lower) are being referred to in each part description. Please clearly describe what is being shown in the upper and lower panels of each column/part of the figure. Please also define the abbreviations for the different planes of view (i.e. ax, sag, cor) and imaging method (i.e. T2WI, T1WI, CE).]**

Box 1. Metabolic syndrome, circulatory effects and mortality.

Hypothalamic dysfunction resulting in morbid obesity greatly impacts QOL but, above all, it increases the risk of developing metabolic syndrome, resulting in excess morbidity and mortality[7,282,303,304]. Metabolic syndrome is an important cardiometabolic risk factor and is defined as the presence of at least 3 of the following manifestations: obesity, insulin resistance, dyslipidaemia and elevated blood pressure. Hypothalamic damage may increase circulating levels of insulin, resulting in increased fat storage and subsequently insulin resistance. In addition, leptin levels are increased in hypothalamic syndrome, which means that the condition resembles leptin resistance. **[Au: Edit OK? Is this what you meant by resembling leptin resistance? Please reference this statement.]** Elevated leptin levels in combination with autonomic nervous system dysfunction leads to obesity and subsequently metabolic derangements that result in metabolic syndrome.

Using BMI as an obesity marker, the prevalence of metabolic syndrome in patients with craniopharyngioma has been estimated to be 46% [148]. If obesity is defined by fat percentage instead of BMI, the frequency of metabolic syndrome is even higher (52%)[305]. In a large cohort analysis ($n = 224$), patients with

craniopharyngioma had excessive total mortality (standardized mortality rate (SMR) 2.7; 95% confidence interval (CI) 2.0–3.8) and mortality due to circulatory disease (SMR 2.3; 95% CI 1.1–4.5) and respiratory disease (SMR 6.0; 95% CI 2.5–14.5). Excess morbidity was also observed, especially due to type 2 diabetes mellitus (standardized incidence rate (SIR) 4.4; 95%, CI 2.8–6.8) and cerebral infarction (SIR 4.9; 95% CI 3.1–8.0) compared with the general population. Risk factors for type 2 diabetes mellitus, cerebral infarction[306] and total mortality included female sex, childhood-onset craniopharyngioma, hydrocephalus and tumour recurrence. Mortality in patients with panhypopituitarism might also be caused by inadequately treated ACTH deficiency. In a cohort study[303], all patients who died from respiratory diseases suffered from secondary adrenal insufficiency. The contribution of adrenal crises in response to acute stress and intercurrent illness to the death of adult patients with hypopituitarism has been described previously [307] and thus adequate glucocorticoid replacement therapy must be a point of attention.

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Box 2. Clinical characteristics of Prader–Willi syndrome

Feeding behaviour problems
Poor feeding with failure to thrive and anorexia in infancy that further switches to unexplained excessive weight gain followed by hyperphagia and deficits of satiety leading to early and severe obesity with impaired body composition comprising increased subcutaneous fat mass, decreased lean mass and decreased resting energy expenditure. **[Au: This text is difficult to follow so I suggest splitting it into bullet points.]**

Endocrine dysfunctions
- Pituitary deficits: Growth hormone deficiency (near 100% short stature), hypogonadism (near 100%) **[Au: the matching closing parenthesis/bracket after this comment is missing.]** (at birth cryptorchidism and micropenis in boys, hypoplasia of labia minora in girls and delayed and uncomplete **[Au: incomplete?]** puberty with infertility in men and rare pregnancies in women, central hypothyroidism (30–80%), extremely rare corticotropin deficit (10%)
- Premature adrenarche (30%) with rare cases of precocious start of puberty
- Hyperghrelinaemia starting at birth and remaining at all ages
- Decrease in number of oxytocin neurons
- High risk of type 2 diabetes mellitus, 25% in case of obesity **[Au:OK?]**

Intellectual disability
- Mild cognitive deficit (mean IQ around 70)
- Delayed psychomotor development age at walking around 2 years
- Learning disabilities
- Language and communication problems with rare cases of true dysarthria
- Poor social abilities and theory of mind, rare cases of confirmed autism spectrum disorder (ASD)
- Poor emotional regulation
- Mood lability and high level of anxiety

41

- Skin picking constant [Au:constant skin picking?] in adolescents and adults
- Psychiatric troubles such as depression and psychosis [Au: Edit OK?]

Dysautonomia
- Respiratory sleep disorders: obstructive sleep apnea syndrome (OSAS) with both central and obstructive apneas
- Sleep disorders: hypersomnia, narcolepsy, cataplexy
- Dysphagia and gastrointestinal disorders
- Hydro-electrolytic disorders: hyponatraemia
- Temperature dysregulation
- Cardiovascular disorders: high heart rate variability, orthostatic hypotension
- Poor and sticky saliva
- Pain insensitivity

Comorbidities
- Hypotonia: possibly from central origin, severe at birth and infancy and remaining although less severe at all ages
- Orthopaedic problems:
     -Scoliosis: 2 peaks before 4 years (30%) and at puberty (50%) [Au: two peaks (1 before 4 and 1 at puberty) or three peaks (2 before 4 and 1 before puberty? please clarify.]
     - Kyphosis, particularly in patients with obesity [Au:OK?]
     - Hip dysplasia in 15% of patients [Au:OK?]
- Epilepsy in 20–30% of patients [Au:OK?]
- Lymphoedema with high risk of erysipelas
- Ocular (myopia, hyperopia, strabismus) and dental problems (impaired tooth enamel)

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