

Diagnostic criteria for the hypothalamic syndrome in childhood

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Abstract

Objective: Hypothalamic syndrome (HS) in childhood is a rare condition. Its epidemiology is not well known because incidence and prevalence are related to very rare underlying diseases. In addition, different criteria for the syndrome are used across studies. Recognizing the HS may be difficult, due to its rareness and variety of symptoms. Having diagnostic criteria for signs and symptoms of hypothalamic dysfunction may aid in early recognition and diagnosis, in the reporting and understanding of its etiology, in predicting its course and its management. We aimed to define diagnostic criteria for hypothalamic dysfunction and a score for the presence of HS in childhood.

Methods: Diagnostic criteria for hypothalamic dysfunction were developed and subdivided into hyperphagia, hypophagia, body mass index, behavioral problems, sleep disorders, temperature regulation disorders, pituitary dysfunction, radiological hypothalamic assessment, and presence/suspicion of a hypothalamic genetic syndrome. Subsequently, the scoring system was tested in a retrospective cohort of 120 patients at risk for hypothalamic dysfunction.

Results: A score for presence of HS was developed. Using this new hypothalamic score, in total 52.5% were scored as having HS. Of these patients, 76.7% were diagnosed with pituitary dysfunction, 32.5% with hyperphagia, 40% with sleep disorders, and 14.2% with temperature dysregulation. For several criteria, clinical data was missing in more than 50% of cases.

Conclusions: The here proposed diagnostic criteria for hypothalamic dysfunction and score for presence of HS may be used for care purposes and to aid in early recognition. Also it will be useful for research or registration purposes.

Keywords: hypothalamic syndrome, child, diagnostic criteria, hypothalamic dysfunction

Significance

The hypothalamic syndrome (HS) in childhood is a rare condition. Children may present with obesity, pituitary dysfunction, sleep disturbances, temperature dysregulation, and/or behavioral problems. Its epidemiology is not well known because different criteria for the syndrome are used across studies. Recognizing the HS may be difficult, due to its rareness and variety of symptoms. Having diagnostic criteria for signs and symptoms for hypothalamic dysfunction may aid in early recognition and diagnosis and in the reporting and understanding of its etiology. In addition, it may aid in predicting its course and in its management. To have a score for presence of the HS may be useful for research or registration purposes.

Introduction

The hypothalamus is the key player of the human's body balance, as it acts as a central integrator for endocrine, autonomic, and higher brain functions.¹ This delicate endocrine organ, located in the suprasellar region of the brain, does not only stimulate the pituitary gland by its releasing hormones, but also regulates temperature stability, salt and water balance, hunger and satiety feelings, and circadian rhythms. The hypothalamus plays an essential role in energy balance. In addition, through its connective circuits, the hypothalamus

also plays a central role in behavior. Hypothalamic malfunction may lead to a variety of symptoms; from sleeping disorders and hyperphagia (abnormal increased hunger feeling) with a normal functioning pituitary gland to severe behavioral problems with morbid obesity and panhypopituitarism with diabetes insipidus (DI).²

Causes of hypothalamic dysregulation in childhood may be genetic, such as in the Prader–Willi syndrome, or acquired, such as in children with suprasellar brain tumors (chiasmatic hypothalamic glioma (CHG), germinoma, craniopharyngioma).^{2–5}

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In addition, hypothalamic dysfunction has been described to occur following cranial radiation for brain tumors and after (repetitive) traumatic brain injury.^{6,7} Also, auto-immune (hypophysitis or hypothalamitis)⁸ or unknown etiologies (such as the Rapid-onset Obesity with Hypoventilation, Hypothalamic, Autonomic Dysregulation, and Neural Endocrine Tumor syndrome (ROHHADNET-syndrome)⁹ may result in hypothalamic dysregulation. All these entities are very rare (incidences ranging from 0.05 to 10 per 100 000 persons per year, Table 1). Symptoms of hypothalamic dysfunction are often not adequately recognized, and therefore delay in diagnosis is repeatedly encountered.¹⁰ This may cause further aggravation of hypothalamic damage or damage to surrounding structures, such as the optic nerve for example, or may cause aggravation of the consequences of hypothalamic damage, such as type 2 diabetes mellitus (DM2) or respiratory failure.¹¹

For these reasons, we first aimed to develop diagnostic criteria, which help to recognize signs (observed by another individual) and symptoms (experienced by the index person) that may be present in children with hypothalamic dysfunction. In addition, we aimed to develop a scoring system for presence of the hypothalamic syndrome (HS) in childhood, which may be used for research purposes or in registries for prevalence of the HS. For this aim, we distinguished three domains in which criteria can be scored; clinical criteria, radiological criteria, and “pre-likelihood” criteria (defined as chance of the child to develop hypothalamic dysfunction based on the medical history of the patient that is already known, such as a genetic diagnosis).

Subsequently, to assess whether it is feasible to perform this new proposed hypothalamic score in current cohorts of patients at risk for hypothalamic dysfunction, the score was tested in 120 patients at risk for hypothalamic dysfunction.

Methods

The development of the diagnostic criteria and hypothalamic score

By combining knowledge on the clinical signs or symptoms of hypothalamic dysfunction² (Table 2) in combination with radiological and genetic criteria, new diagnostic criteria were developed for hypothalamic dysfunction (Table 3). The diagnostic criteria were subdivided into hyperphagia, hypophagia, body mass index (BMI), behavioral problems, sleep disorders, temperature regulation disorders, and pituitary dysfunction. In addition to the clinical criteria, radiological criteria were

also defined and a “pre-test probability” for having hypothalamic dysfunction (presence or suspicion of a hypothalamic genetic syndrome).

Feasibility of the novel hypothalamic score

To assess whether it is feasible to perform this new proposed hypothalamic score in current cohorts of patients at risk for hypothalamic dysfunction, the score was tested in 120 patients. Patients were randomly selected from three databases; the Dutch Childhood Craniopharyngioma Cohort ($n=30$), the Dutch Childhood Suprasellar LGG cohort ($n=30$), and the German KRANIOPHARYNGEOM 2007 and Registry 2019 ($n=60$).

Patients were selected based on age (≤ 18 years at moment of diagnosis) and follow-up time (>2 years). Follow-up time was chosen to be minimal 2 years after diagnosis of the brain tumor, because it has been shown that significant increases in BMI occur during the early (post-operative) period especially during the first years after diagnosis.²³ Due to the retrospective design, no questionnaires were used but scoring was done based on data retrieved from the medical records. Best available data at last moment of follow-up were used. If a criterion was not reported in the medical chart, it was regarded as missing. Due to the fact that the Muller Score has originally been developed for craniopharyngioma and not for low-grade glioma (LGG), for children with LGG, next to the Muller Score also the Dodge criteria were scored. The Dodge classification is used for description of the anatomic location of optical pathway glioma's.²⁴ No correlation, however, was found between the Dodge criteria and hypothalamic signs or the Muller criteria (data not shown) and it was chosen to also use the Muller criteria for children with LGG in this hypothalamic scoring system.

Ethics

The study protocol of KRANIOPHARYNGEOM 2007 was proven and accepted by the ethical committee of the University of Würzburg, Germany; the protocol of KRANIOPHARYNGEOM Registry 2019 by the ethical committee of the Carl von Ossietzky University Oldenburg, Germany. The study protocols for Dutch craniopharyngioma and suprasellar LGG patients were shared with the Medical Research Ethics Committee, Utrecht, who ruled that no procedures were required regarding human subject safety since only secondary, anonymized data were used.

Table 1. Etiology of the hypothalamic syndrome in children.

Condition	Incidence range (per 100 000 persons per year)	%	Cohort
Craniopharyngioma	0.12-0.21	50	Pediatric
Germ cell tumor	0.06-0.09	30	Pediatric/adult population
Chiasmatic hypothalamic glioma	3.00-4.00	80	Pediatric
Rathke's cleft cyst	0.51%-3.5% of sellar and parasellar lesions	20	Pediatric/adult population
Langerhans cell histiocytosis	0.46-0.89	20	Pediatric
Prader-Willi syndrome	3.30-10.00	100	Pediatric/adult population
Septo-optic dysplasia	0.05	20	Pediatric/adult population
ROHHADNET syndrome	100 cases reported worldwide	100	Pediatric/adult population

Conditions in which HS have been described. Modified from Muller et al.² In addition to the above-mentioned etiologies, hypothalamic dysfunction has also been described following cranial radiation therapy for brain tumors and following (repetitive) brain injury.^{6,7} HS, hypothalamic syndrome; ROHHADNET, Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, and neural endocrine tumor.

All patients or custodians were informed according to the study protocols and gave informed consent.

All research performed complies with the Declaration of Helsinki.

Results

Clinical criteria for diagnosis of the hypothalamic syndrome

The clinical signs or symptoms of hypothalamic dysfunction (Table 2) depend on its etiology, on the nuclei that are involved, and on the age of the patient. Each clinical sign or symptom can be subdivided with regard to degree of severity, making the hypothalamus as underlying cause more or less likely.

Hyperphagia

The ventromedial hypothalamus (VMH), arcuate nucleus (AN), and periventricular nucleus (PVN) located in the hypothalamus regulate hunger, satiety, and energy balance.^{15,25,26} The hypothalamic nuclei receive signals from peripheral hormones (leptin, insulin, ghrelin, neuropeptide Y), which are produced by adipocytes, the islet cells, and the gut after food intake (satiety hormones) (Figure 1). When the VMH, AN or PVN are damaged, the signals of the peripheral hormones cannot be properly integrated, which results in an increased hunger feeling with subsequent caloric intake.²⁷ Also, due to damage to the efferent pathways, energy expenditure may be decreased. The combination of increased hunger feelings with decreased energy expenditure causes weight gain, which can be extreme and rapid. Severe hyperphagia has been described in amongst others children with Prader–Willi syndrome, Smith Magenis syndrome, hypothalamic hamartoma, craniopharyngioma and chiasmatic hypothalamic glioma.^{28–32}

Most children with (general) obesity also have an increased caloric intake, which may be interpreted as hyperphagia, however just a small percentage of these children have true hyperphagia caused by hypothalamic dysfunction.³³ A distinction may be made between those children whose hyperphagia can be controlled by adequate parenting styles or those who cannot be controlled by any means. In the latter, the hyperphagia can disrupt family life, with children stealing food from class mates or from the refrigerator, requiring 24/7 supervision. To objectify the presence of hyperphagia, the Dykens Hyperphagia Questionnaire may be used.¹² This questionnaire has been developed for children with the Prader–Willi syndrome, and consists of a 13-item informant measure.^{12,34} In children with increasing hyperphagia (and obesity) in time, hypothalamic dysfunction must be suspected for which additional diagnostics, such as cerebral imaging or genetic analysis, is recommended.

Hypophagia/failure to thrive (diencephalic syndrome)

In contrast to the above described hyperphagia, young children with hypothalamic damage, may present with the diencephalic syndrome (DS). This phenomenon resulting in hypophagia is observed in young children with Prader–Willi syndrome, and also in young children (newborn until the age of 4) with craniopharyngioma or suprasellar LGG.^{28,32,35,36} The underlying pathophysiology for DS is not fully understood. Current hypotheses for weight loss focus on loss of appetite, increased energy expenditure, and

Table 2. Clinical signs and symptoms of the hypothalamic syndrome.

	Diagnosis	Clinical sign or symptom
Eating disorders ^a	Hyperphagia	Extensive hunger, binge-eating, overweight or obesity
	Hypophagia	Failure to thrive, underweight
Behavioral disorders ^b	Obsessive compulsive symptoms	Fixate on certain topics, repetitive behavior or rituals, difficulty with changes
	Hoarding	Collecting items not needed
Sleep disorder ^c	Rage	Uncontrollably angry
	Sleep apnea	Snoring, fatigue
	Hypersomnia/insomnia	Daytime sleepiness
	Falling asleep at random places during the day	Falling asleep at random places during the day
	Frequently wake at night	Frequently wake at night
Temperature regulation disorders ^d	Waking up extreme early	Waking up extreme early
	Hypothermia	Cold feeling, shivering
	Hyperthermia	Temperature < 36 °C
	Temperature dysregulation	Temperature > 37.5 °C without infection
Endocrine dysfunction	Frequently cold or warm hands, feet and face (cheeks) at unusual moments	Frequently cold or warm hands, feet and face (cheeks) at unusual moments
	Central precocious puberty	Girls: Tanner stage B2 < 8 years of age
		Boys: Testicular volume ≥ 4 ml < 9 years of age
	GH deficiency	Decreased growth velocity/short stature
	TSH deficiency	Fatigue, decreased growth velocity, increasing BMI
	ACTH deficiency	Hypoglycemia, prolonged fever, abdominal or head aches
	LH/FSH deficiency	Late puberty/no pubertal development
	Diabetes insipidus with/without adipsia	Polyuria/polydipsia

^aHyperphagia defined as extensive hunger/food obsession, binge-eating. To objectify the presence of hyperphagia, the Dykens Hyperphagia Questionnaire¹² may be used.

^bBehavioral problems defined as presence of obsessive compulsive symptoms (defined as fixate on certain topics, repetitive behavior or rituals, difficulty with changes), hoarding (collects items not needed), rage. To objectify behavior, the Prader–Willi Syndrome Behavior Questionnaire¹³ may be used.

^cSleep disorder symptoms defined as difficulty falling asleep, daytime sleepiness or falling asleep at random places during the day, regularly waking up extreme early or diagnosed with sleep apnea. For assessment, history taking, the Epworth Scale criteria,¹⁴ actigraphy, and PSG may be used.

^dTemperature regulation disorder symptoms defined as presence of (episodes of) hypothermia or hyperthermia, or a story of frequently cold or warm hands, feet, and face (cheeks) at unusual moments. For assessment of body temperature, core temperature may be measured during several days at fixed times.

increased lipolysis by pituitary B-lipotropin has been suggested, caused by growth hormone (GH) overproduction with partial GH resistance which is found in some children.^{37–39} The fact that hypothalamic hypophagia is mainly seen in young children may be due to the fact that the hypothalamus matures during childhood and thus hypothalamic dysfunction may result in different outcomes, depending on age.³² Hypophagia and anorexia have, however, also been described in older children and even in adults with suprasellar tumors, such as craniopharyngioma.⁴⁰

Table 3. Proposed diagnostic criteria for presence of the hypothalamic syndrome.

	Score	Total score
Clinical criteria		
Hyperphagia ^a	0 = no 1 = mild (can be controlled by parental restriction or patient itself) 2 = mild after specific intervention for hyperphagia OR severe (cannot be controlled by parents or patient itself or steals food)	1 = minor criterion 2 = major criterion
Hypophagia/failure to thrive (diencephalic syndrome)	0 = no 1 = mild (can be stimulated to eat by parents/caregivers) 2 = severe (cannot be stimulated to eat by parents/caregivers or requires tube feeding for eating)	1 = minor criterion 2 = major criterion
Body mass index (kg/m ²) ^b	0 = Normal weight or overweight (BMI using the Cole criteria, or age and gender specific) 2 = Normal weight after specific intervention for hypothalamic obesity OR overweight after specific intervention for hypothalamic obesity** OR obesity (BMI using the Cole criteria* or age and gender specific)	2 = major criterion
Behavioral problems ^c	0 = none 1 = mild (can be corrected by parents/caregivers) OR score > 22.2 on PWSBQ 2 = mild after specific intervention for hypothalamic behavioral problems OR severe (cannot be corrected by parents/caregivers, requires specialist treatment) OR score > 55.7 on PWSBQ	1 = minor criterion 2 = major criterion
Sleep disorder ^d	0 = no, Epworth Scale score 0-10 1 = mild (one or more sleep symptoms without disruption of school and/or family) OR Epworth Scale score 11-17 2 = mild after specific intervention such as melatonin OR severe (disrupts school and/or family, diagnosis of obstructive sleep apnea syndrome OR Epworth Scale score > 18)	1 = minor criterion 2 = major criterion
Temperature regulation disorder ^e	0 = no 1 = mild, core-temperature multiple times between 35 and 36 °C or above 37.5 °C 2 = severe (needs intervention such as specialized heat clothing), core-temperature measured below < 35 °C	1 = minor criterion 2 = major criterion
Pituitary dysfunction ^f	0 = no pituitary dysfunction 1 = partial or complete pituitary dysfunction (with or without DI (with adequate thirst feeling) or SiADH) OR history of central precocious puberty 2 = (partial or complete) pituitary dysfunction including DI and adipsia, (inadequate thirst feeling)	1 = minor criterion 2 = major criterion
Radiological (MRI) criteria (for children with suprasellar tumors)		
Müller grading ^g	0 = grade 0: no hypothalamic involvement or lesion; 1 = grade I: hypothalamic involvement or lesion of the anterior hypothalamus that does not involve the hypothalamic area of the mammillary bodies and beyond; 2 = grade II: hypothalamic involvement or lesion of the anterior and posterior hypothalamic area	1 = minor criterion 2 = major criterion
Pre-test probability (for children with no suprasellar tumors)		
Genetic syndrome or diagnosis present?	0 = no known genetic syndrome or diagnosis associated with hypothalamic dysfunction 1 = genetic syndrome or diagnosis present which may be associated with hypothalamic dysfunction (eg, Smith–Magenis syndrome) 2 = genetic syndrome or diagnosis present of which has been proven to be associated with hypothalamic dysfunction, such as Prader–Will syndrome or ROHHADNET	1 = minor criterion 2 = major criterion

Hypothalamic syndrome (HS) may be considered present in case:

≥3 major criteria OR.

“At least” four minor criteria OR.

“At least” one minor radiological and two major OR.

Two major and “at least” two minor OR.

One major radiological and major obesity OR.

One major radiological criterion and “at least” two minor criteria.

Note 1: For most criteria objective questionnaires are recommended. When this is not feasible, for instance when retrospective analysis is done for research purposes, more subjective criteria may be used.

Note 2: It must be noted that when the score is used for assessing presence of the HS at a certain point in time, the criteria may be adjusted for any intervention as given specifically for the hypothalamic sign or symptom (eg, BMI gives a score 0 when overweight with no intervention but score 2 when overweight after specific intervention for hypothalamic obesity).

Note 3: When the scoring system is used for the evaluation of hypothalamic dysfunction in time, the clinical signs or symptoms should be scored as present before the specific intervention.

^aHyperphagia defined as extensive hunger/food obsession, binge-eating. To objectify the presence of hyperphagia, the 13-item Dykens Hyperphagia Questionnaire may be used.^{12,15}

^bUnderweight, overweight, and obesity in infant CBTS (0-2 years) is defined according to the international cut-off points of the World Health Organization using BMI < -2.0 SDS, BMI > 2.0 SDS, and BMI > 3.0, respectively.¹⁶ Underweight, overweight, and obesity for CBTS aged ≥2 years were defined according to the international cut-off points of Cole et al., using BMI thinness grade 2 (equal to a z-score of -2), and the international cut off points of BMI by sex and age for overweight and obesity.^{17,18}

^cSpecific intervention for hypothalamic obesity includes treatment with dextro-amphetamine, caffeine and ephedrine-HCl, mazindol, methylphenidate, octreotide, diazoxide and metformin, beloranib, exenatide, liraglutide tesomet, oxytocin and naltrexone, carbetocin or bariatric surgery.²

^dBehavioral problems defined as presence of obsessive compulsive symptoms (defined as fixate on certain topics, repetitive behavior or rituals, difficulty with changes), hoarding (collects items not needed), rage. Behavioral problems can be assessed using the PWS Behavioral Questionnaire (PWSBQ) or available neuropsychological investigation data may be used as a surrogate for hypothalamic dysfunction-related behavioral problems.¹⁹

^eSleep disorder symptoms defined as difficulty falling asleep, daytime sleepiness or falling asleep at random places during the day, regularly waking up extreme early or diagnosed with sleep apnea. For further assessment, history taking, the Epworth Scale criteria,^{14,20} actigraphy and PSG may be used.

^fTemperature regulation disorder defined as presence of (episodes of) hypothermia or hyperthermia, or a story of frequently cold or warm hands, feet and face (cheeks) at unusual moments. For assessment of body temperature, core temperature may be measured during several days at fixed times. Grading is done according to the CTC system: CTC grade 1: mild (a story of frequently cold or warm hands, feet, and face at unusual moments. A story of: “my child never makes fever”). CTC grade 2: moderate (35-36 °C or hyperthermia). CTC grade 3: severe (33-35 °C). CTC grade 4: life-threatening (<33 °C).²¹

^gPartial hypopituitarism is defined as any anterior pituitary disorder (eg, growth hormone deficiency (GHD), thyroid-stimulating hormone deficiency (TSHD), adrenocorticotrophic hormone deficiency (ACTHD), gonadotrophin-releasing hormone deficiency (GnRHD), hyperprolactinemia or syndrome of inappropriate ADH secretion (SiADH)).

^hHypothalamic damage in children with a suprasellar brain tumor may be scored on MRI using the Muller grading consisting of: grade 0: no hypothalamic involvement, grade I: hypothalamic involvement of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, grade II: hypothalamic involvement of the anterior and/or solely posterior hypothalamic area, ie, involving the area beyond the mammillary bodies.²²

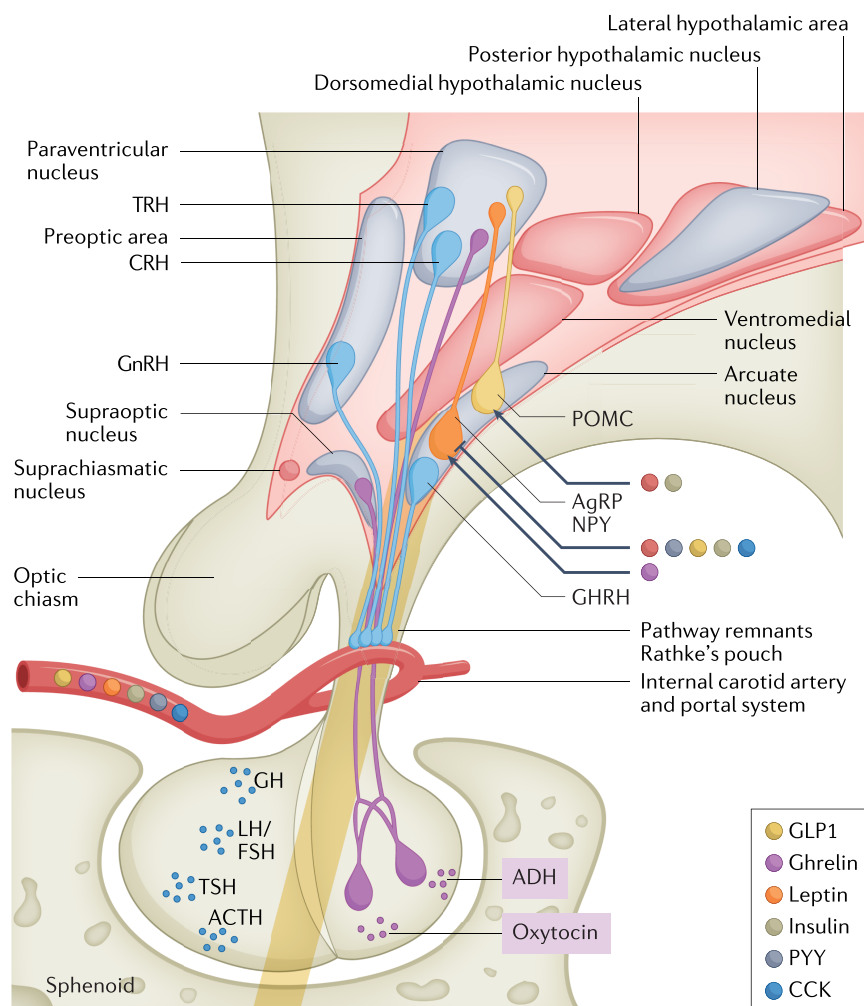


Figure 1. Schematic overview of the nuclei in the human hypothalamus. The hypothalamus consists of many hypothalamic nuclei, which are all highly connected through neural pathways. The connection between the AN and paraventricular nucleus is emphasized. Afferent and efferent blood vessels provide a pipeline for pituitary hormones, as well as hunger and satiety hormones that stimulate hypothalamic neuron orexigenic and anorexigenic responses, respectively. AN, arcuate nucleus; CRH, corticotropin-releasing hormone; DM, dorsomedial hypothalamic nucleus; OC, optic chiasm; PA, preoptic area; PH, posterior hypothalamic nucleus; SCN, suprachiasmatic nucleus; SO, supraoptic nucleus; VMN, ventromedial hypothalamus. *Source:* © 2019 Illustration Presentation ENDOCRINE SOCIETY.¹²

Body mass index

Parallel to the change in eating behavior, changes in BMI are observed. The typical picture regarding energy homeostasis after hypothalamic damage is increase in BMI (overweight). Underweight is much more rare and mainly seen in the very young children with suprasellar LGG or Prader–Willi syndrome and in very rare cases also in craniopharyngioma, presenting with hypophagia.^{28,32,41}

Body mass index may not only increase due to increased intake, increase in BMI may also be seen without the presence of hyperphagia, due to decreased resting energy expenditure (REE) presumably caused by disturbance of the autonomic nervous system and a state of leptin resistance.^{42,43}

Next to hyperphagia and decreased REE, children with the HS may have low hormonal levels including pituitary hormones, low insulin-like growth factor-1 (IGF-1), and low thyroxine concentrations, contributing to a deprived metabolic state and increase of BMI. In case of adrenocorticotrophic hormone (ACTH) deficiency and hydrocortisone maintenance therapy, weight gain may be influenced by the need for higher doses of maintenance dosage or frequent increased stress dosages of hydrocortisone.

In addition, other factors for an increasing BMI may be present, such as decreased mobility, as a consequence of visual or neurological damage contributing to low total energy expenditure, excessive sleep or due to loss of initiative.

Behavioral problems (obsessive compulsive symptoms, hoarding, rage)

In children with hypothalamic dysfunction, behavioral problems can be present. These are hypothesized to be due to damage to the connective circuits of the hypothalamic regions and the Papez circuit, which connects the hypothalamus to the limbic lobe^{44–46} (Figure 2). Damage to the Papez circuit may lead to problems in control anxiety or memory problems; children may repeatedly ask for the day planning or get upset when plans suddenly change.⁴⁷ Damage to the nucleus accumbens may lead to addiction or obsession; children with severe hypothalamic damage often demonstrate the urge for hoarding or collecting items in excessive amounts.⁴⁸

To assess behavioral, neurocognitive or emotional dysfunction, validated and specific questionnaires may be used, such as the Prader–Willi Syndrome Behavior Questionnaire.^{13,19}

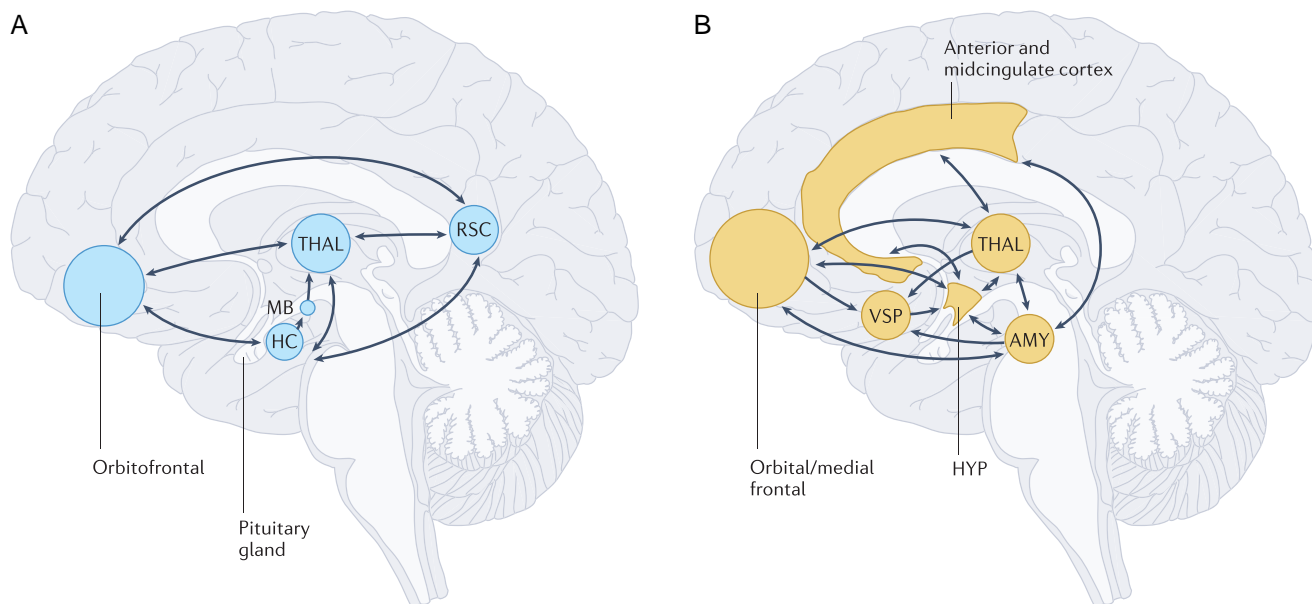


Figure 2. Structures in the brain involved the neurocognitive consequences seen in patients with hypothalamic damage. The hypothalamus is an integral part of two different networks of the limbic system: a hippocampus (HC)-centered network essential for episodic memory (A) and an amygdala (AMY)-centered network relevant for social-emotional functioning (B). Damage to brain regions within these networks or to their connecting fibers contributes to the neurobehavioral and psychiatric abnormalities in 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 fibers: fornical fibers projecting from the hippocampus to the MB, or fibers of the mammillothalamic tract projecting from the MB to the anterior thalamic nucleus (A). Deficits in social-emotional functioning in HS may result from lesions to hypothalamic nuclei anterior to the MB and, for example, from tumor-related or treatment-related damage to other regions of the AMY-centered network (B). RSC, retrosplenial cortex; THAL, thalamus; VSP, ventral striatopallidum.²

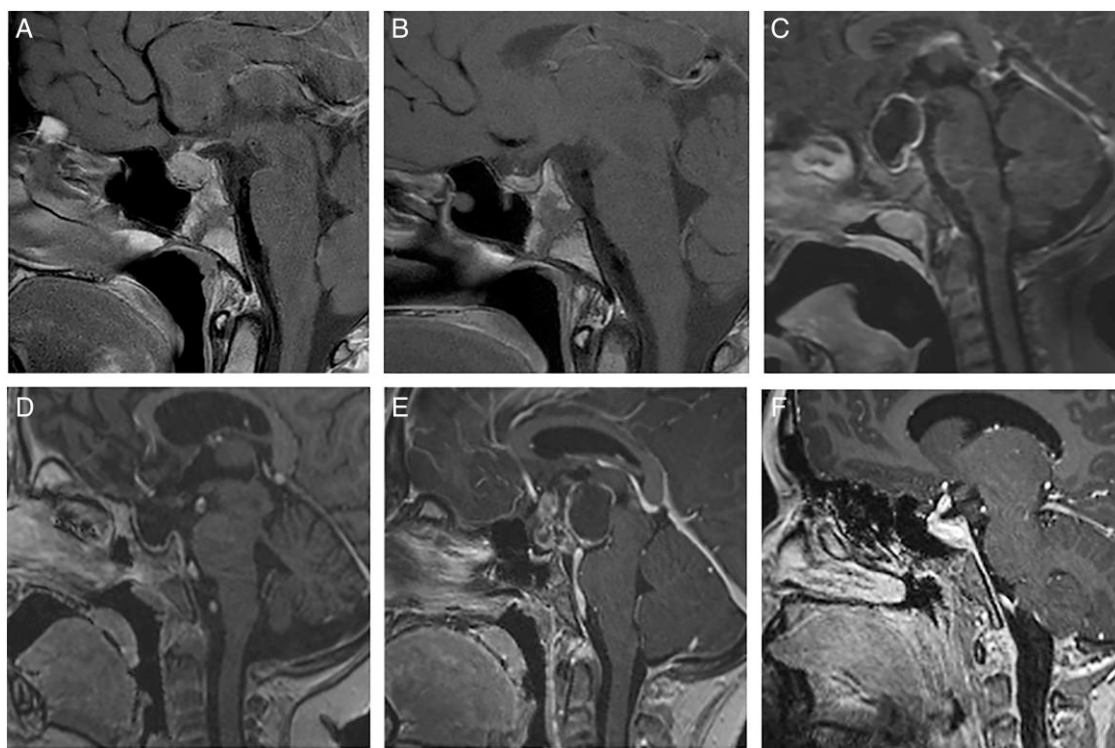


Figure 3. Radiological assessment of hypothalamic damage. Pre- and post-operative MRI images with classification of craniopharyngioma according to the degree of hypothalamic involvement/surgical lesions using the Muller score.¹⁵ (A/B) Grade 0 (0°), no hypothalamic involvement/lesion. (C/D) Grade 1 (I°), hypothalamic involvement/lesion of the anterior hypothalamus not involving the mammillary bodies and the hypothalamic area beyond mammillary bodies. (E/F) Grade 2 (II°), hypothalamic involvement/lesion of the anterior and posterior hypothalamic area, ie, involving the mammillary bodies and the area beyond mammillary bodies.

Intelligence is most often not affected but school achievements may decline due to the concentration disruption, memory loss, or behavioral problems. Also complaints of (chronic) fatigue may hinder learning capabilities. Children with HS and behavioral problems need psychosocial support that should be provided by an expert team with expertise on hypothalamic neurocognitive consequences. Its management may be difficult and may require additional psychiatric support.

Sleep disorders

The suprachiasmatic nuclei (SCN) in the hypothalamus regulates the human circadian rhythm, controlling both wake and sleep.⁴⁹ The pineal gland produces melatonin, which is produced mainly in the dark and in turn influences this hypothalamic rhythm.⁵⁰ In children with hypothalamic dysfunction, the melatonin production or response to melatonin can be aberrant.²⁰ Next to the SCN, sleep is also regulated (promoted) by the ventrolateral preoptic nucleus (VLPO) and the lateral hypothalamus area (LHA), together with the monoaminergic cell groups (MCG) (arousal) system.⁵¹ These pathways interact and promote the transition between wake and sleep. Damage to the VLPO may result in insomnia and damage to the LHA may result in both sleep disruption, as well as daytime sleepiness.⁵²⁻⁵⁴ In children with hypothalamic obesity following craniopharyngioma treatment, presence of secondary narcolepsy was suggested.⁵⁴ Children with obesity may develop the sleep apnea syndrome for which night ventilation may be indicated. Next to hypothalamic causes of disturbed sleep, also other causes may be present such as visual loss, irregular bedtime routine, or social factors.⁵⁵

The assessment of sleep disorders may be done by performing a sleep history, preferably using a sleep questionnaire suitable for the age.^{55,56} For the degree of daytime sleepiness the Epworth Sleepiness Scale (ESS) may be used.^{14,21,54} Subsequently, actigraphy may be used for objective sleep wake rhythm evaluation, including sleep onset latency, sleep efficiency, total sleep time and wake after sleep onset.⁵⁵ Presence of sleep apnea may be confirmed by polysomnography (PSG) with capnography.

Temperature dysregulation

The hypothalamus is essential for body temperature regulation.⁵⁷ The AN regulates thermogenesis (increases heat production) through brown adipose tissue (BAT) by nutritional cues, hormonal signals (leptin and insulin) or temperature changes.^{22,58} In addition, the preoptic area (PA)–dorsomedial nucleus of the hypothalamus (DMH) circuit receives sensory input from temperature-sensitive neurons. Also, the VMH is an important nucleus involved in cold-induced thermogenesis by controlling BAT. The fact that the action of thyroid hormones is required to maintain the correct body temperature during cold exposure, which is regulated through the hypothalamus–pituitary–thyroid axis, illustrates the role of the hypothalamus (especially the PVN by production of thyrotropin-releasing hormone (TRH)) in the regulation of adaptive thermogenesis during cold exposure.⁵⁷

When the hypothalamus malfunctions, patients may thus develop temperature dysregulation resulting in (episodes of) hypothermia (temperature below 36 °C) or (episodes of) hyperthermia (temperature above 37.5°C). Hypothermia may subsequently result in fatigue, lower energy expenditure, and may affect thyroid, GH, and hydrocortisone metabolism.

Due to sympathetic dysregulation, patients may experience cold hands and flushed cheeks, despite having a normal body temperature.

Temperature dysregulation may be diagnosed by measurement of the core temperature, preferably by charting a basal temperature curve for several days with additional measurements of the core temperature at moments of feeling cold, hot or fatigue.

Pituitary dysfunction

The hypothalamic releasing hormones (growth hormone-releasing hormone, GHRH; gonadotrophin-releasing hormone, GnRH; TRH; and corticotropin-releasing hormone, CRH) stimulate the anterior pituitary gland to produce and secrete the pituitary hormones (GH, luteinizing hormone and follicle-stimulating hormone (LH/FSH), thyroid-stimulating hormone (TSH), and ACTH), which in turn have their own peripheral actions. Vasopressin is produced in the hypothalamus and stored in the posterior pituitary gland. Dependent on its etiology and severity, children with the hypothalamic syndrome may present with an adequate functioning pituitary gland or with (partial) pituitary insufficiency with or without DI. Children with most severe hypothalamic damage develop pan-hypopituitarism with no adequate thirst regulation requiring 24/7 surveillance of salt and fluid balance. In young children with chiasmatic hypothalamic glioma, the GH hypersecretion (GHH) syndrome may be present resulting in elevated IGF-1 concentrations,⁵⁹ and sometimes increased linear growth. The etiology of GHH in children with CHG has not been elucidated yet. Suggested etiologies for GHH are decreased inhibition of somatostatin, ectopic secretion of GHRH, and it has been associated to early activation of the gonadal axis.⁶⁰ In addition, GH dysregulation may be associated with hypercortisolism and ghrelin production, comparable to the pathomechanism of anorexia nervosa.⁶¹ Young children with hypothalamic dysfunction are at risk to develop central precocious puberty, due to early activation of the hypothalamic–pituitary gonadal axis, especially those with CHG (and neurofibromatosis 1, NF1), hypothalamic hamartoma, or those having been exposed to a period of increased intracranial pressure.¹⁶

Radiological criteria

There are several radiological scoring systems that can be used for assessing hypothalamic damage.¹⁷ For pre- and post-operative children with craniopharyngioma, the Müller radiological score has been developed to assess the degree of hypothalamic damage (Figure 3); 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 (ie, involving the mammillary bodies and the area beyond).¹⁸ This scoring system may also prove to be useful for other suprasellar tumors.²² The severity of radiological damage is, however, not always related to the clinical grade of hypothalamic damage or to the presence of obesity, for this reason, also clinical criteria must be present to accurately diagnose the hypothalamic syndrome.

“Pre-test probability” criteria

When a child presents with obesity, the differential diagnosis is broad with “general” obesity being most probable. When a

Table 4. Assessment of hypothalamic score in 120 patients following treatment for a suprasellar brain tumor.

Criterion	Dutch CP cohort, Registry 2022 N = 30	Dutch LGG cohort Registry 2022 N = 30	KRANIOPHARYNGEOM Registry 2007 and 2019 N = 60
Hyperphagia ^a			
0	n = 14 (46.7%)	n = 18 (60.0%)	n = 12 (20.0%)
1	n = 10 (33.3%)	n = 4 (13.3%)	n = 11 (18.3%)
2	n = 6 (20.0%)	n = 2 (6.7%)	n = 6 (10.0%)
Missing	n = 0 (0.0%)	n = 6 (20.0%)	n = 31 (51.7%)
Hypophagia/failure to thrive (diencephalic syndrome or anorexia)			
0	n = 29 (96.7%)	n = 24 (80%)	n = 25 (41.7%)
1	n = 0 (0.0%)	n = 0 (0.0%)	n = 2 (3.3%)
2	n = 1 (3.3%)	n = 4 (13.3%)	n = 2 (3.3%)
Missing	n = 0 (0.0%)	n = 2 (6.7%)	n = 31 (51.7%)
Body mass index (kg/m ²) ^b			
0	n = 22 (73.3%)	n = 20 (66.7%)	n = 39 (65.0%)
2	n = 8 (26.7%)	n = 10 (33.3%)	n = 21 (35.0%)
Missing	n = 0 (0.0%)	n = 0 (0.0%)	n = 0 (0.0%)
Behavioral problems ^c			
0	n = 14 (46.7%)	n = 9 (30.0%)	n = 6 (10.0%)
1	n = 10 (33.3%)	n = 9 (30.0%)	n = 7 (11.7%)
2	n = 3 (10.0%)	n = 3 (10.0%)	n = 2 (3.3%)
Missing	n = 3 (10.0%)	n = 9 (30.0%)	n = 45 (75.0%)
Sleep disorder ^d			
0	n = 19 (63.3%)	n = 14 (46.7%)	n = 10 (16.7%)
1	n = 8 (26.7%)	n = 15 (50.0%)	n = 11 (18.3%)
2	n = 3 (10.0%)	n = 0 (0.0%)	n = 11 (18.3%)
Missing	n = 0 (0.0%)	n = 1 (3.3%)	n = 28 (46.7%)
Temperature regulation disorder ^e			
0	n = 11 (36.7%)	n = 4 (13.3%)	n = 22 (36.7%)
1	n = 6 (20.0%)	n = 5 (16.7%)	n = 3 (5.0%)
2	n = 0 (0.0%)	n = 2 (6.7%)	n = 1 (1.7%)
Missing	n = 13 (43.3%)	n = 19 (63.3%)	n = 34 (56.7%)
Pituitary dysfunction ^f			
0	n = 2 (6.7%)	n = 23 (76.7%)	n = 3 (5.0%)
1	n = 26 (86.7%)	n = 6 (20.0%)	n = 55 (91.7%)
2	n = 2 (6.7%)	n = 1 (3.3%)	n = 2 (3.3%)
Missing	n = 0 (0.0%)	n = 0 (0.0%)	n = 0 (0.0%)
Müller grading ^g			
0	n = 5 (16.7%)	n = 7 (23.3%)	n = 2 (3.3%)
1	n = 9 (30.0%)	n = 12 (40.0%)	n = 15 (25.0%)
2	n = 15 (50.0%)	n = 11 (36.7%)	n = 43 (71.7%)
Missing	n = 1 (3.3%)	n = 0 (0.0%)	n = 0 (0.0%)
Presence of HS	n = 15 (50.0%)	n = 12 (40.0%)	n = 36 (60.0%)

Feasibility for using the Hypothalamic Scoring System was evaluated in randomly selected patients from three databases; the Dutch Childhood Craniopharyngioma Cohort ($n = 30$), the Dutch Childhood Suprasellar LGG cohort ($n = 30$), and the KRANIOPHARYNGEOM 2007 and Registry 2019 ($n = 60$).

^aHyperphagia defined as extensive hunger/ food obsession, binge-eating. To objectify the presence of hyperphagia, the 13-item Dykens Hyperphagia Questionnaire may be used 31.

^bUnderweight, overweight and obesity in infant CBTS (0-2 years) is defined according to the international cut-off points of the World Health Organization using BMI 2.0 SDS and BMI > 3.0 respectively. Underweight, overweight and obesity for CBTS aged ≥ 2 years were defined according to the international cut-off points of Cole et al., using BMI thinness grade 2 (equal to a z-score of -2), and the international cut off points of body mass index by sex and age for overweight and obesity. 17,18,63

^cBehavioural problems defined as presence of obsessive compulsive symptoms (defined as fixate on certain topics, repetitive behaviour or rituals, difficulty with changes), hoarding (collects items not needed), rage. Behavioural problems can be assessed using the PWS Behavioral Questionnaire (PWSBQ) or available neuropsychological investigation data may be used as a surrogate for hypothalamic dysfunction-related behavioural problems 46.

^dSleep disorder symptoms defined as difficulty falling asleep, daytime sleepiness or falling asleep at random places during the day, regularly waking up extreme early or diagnosed with sleep apnea. For further assessment, history taking, the Epworth Scale criteria, actigraphy and polysomnography may be used 56.

^eTemperature regulation disorder defined as presence of (episodes of) hypothermia or hyperthermia, or a story of frequently cold or warm hands, feet and face (cheeks) at unusual moments. For assessment of body temperature, core temperature may be measured during several days at fixed times. Grading is done according the CTC system: CTC grade 1: mild (a story of frequently cold or warm hands, feet and face at unusual moments. A story of: "my child never makes fever".) CTC grade 2: moderate (35-36 degrees or hyperthermia) CTC grade 3: severe (33-35 degrees) CTC grade 4: life-threatening (<33 degrees) 19.

^fPartial hypopituitarism is defined as any anterior pituitary disorder (e.g. growth hormone deficiency (GHD), thyroid-stimulating hormone deficiency (TSHD), adrenocorticotropic hormone deficiency (ACTHD), gonadotrophin releasing hormone deficiency (GnRHD), hyperprolactinemia or syndrome of inappropriate ADH secretion (SiADH)).

^gHypothalamic damage in children with a suprasellar brain tumor may be scored on MRI using the Muller grading consisting of: grade 0: no hypothalamic involvement, grade I: hypothalamic involvement of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, grade II: hypothalamic involvement of the anterior and/or solely posterior hypothalamic area, i.e. involving the area beyond the mammillary bodies 15.

child, known with the Prader–Willi syndrome, develops obesity, the pre-test probability that this obesity is associated with hypothalamic dysfunction is increased. This pre-test probability is a major criterion for the diagnosis of the HS in a child. The probability increases when a specific diagnosis that may result in hypothalamic obesity, such as the diagnosis of Prader–Willi syndrome or ROHHADNET has been made. For some genetic syndromes, an association with hypothalamic dysfunction has been made in literature but may be less clear, such as in the Smith–Magenis syndrome.⁶² For this reason, such diagnoses are scored as “minor” pre-test diagnoses, as these diagnoses by itself will increase the “pre-test probability” of a child to develop the hypothalamic syndrome, but to a lesser degree than a diagnosis that has been clearly proven to cause hypothalamic dysfunction.

Proposed diagnostic criteria for the presence of the hypothalamic syndrome

By combining the clinical criteria with the radiological criteria and the “pre-test probability” criteria, we have developed a novel score to assess the presence of the HS in pediatric cohorts. Hypothalamic syndrome may be considered to be present in case of (Table 3):

- presence of greater than or equal to three major criteria, or
- “at least” four minor criteria, or
- “at least” one minor radiological and two major criteria, or
- two major and “at least” 2 minor criteria, or
- two major radiological and major obesity, or
- one major radiological criterion and “at least” two minor criteria.

Feasibility of the proposed hypothalamic score

To test its feasibility, the score was explored in our retrospective cohorts with patients at risk for hypothalamic dysfunction after the treatment for craniopharyngioma ($n=30$ Dutch cohort, $n=60$ German cohort) or suprasellar LGG ($n=30$, Dutch cohort). In the Dutch craniopharyngioma cohort, 33.3% of the patients were male (10/30), median age at diagnosis was 5.6 years (IQR 3.5–8.5), median follow-up time was 5.3 years (IQR 4.5–7.4), 100% had been treated with neurosurgery and 60% (18/30) had received radiotherapy, median dose 54 Gy (IQR 54.0–54.0). In the German craniopharyngioma cohort, 58.3% of the patients were male (35/60), median age at diagnosis was 6.0 years (IQR 3.3–9.7), median follow-up time was 5.8 years (IQR 3.4–8.2), 100% of the patients were treated with neurosurgery and 51.7% were treated with radiotherapy (31/60), median dose 54.0 Gy (IQR 54.0–54.0). In the Dutch LGG cohort, 46.7% of the patients were male (14/30), median age at diagnosis was 3.5 years (IQR 1.3–5.8), median follow-up time was 5.7 years (IQR 3.3–9.0), 43.3% of the patients were treated with neurosurgery (13/30), and none received radiotherapy (0%).

As shown in Table 4, with this new hypothalamic scoring system, in total 63/120 (52.5%) of patients were scored as having HS at last follow-up (50% ($n=15/30$) of Dutch craniopharyngioma, 40% ($n=12/30$) of glioma, and 60% ($n=36/60$) of German craniopharyngioma, respectively. Of these patients, in total 76.7% (92/120) were diagnosed with pituitary dysfunction and 32.5% (39/120) had been recognized for

having any degree of hyperphagia, of which 6.7%–20.0% with severe hyperphagia. Within the three cohorts, 23.3%–35.0% of patients had severe obesity, 15.0%–43.3% any degree of behavioral problems, 36.6%–50.0% any degree of sleep disorders and in 14.2% (17/120) or in 6.7%–23.4% of the separate cohorts any degree of temperature dysregulation had been noted. For several clinical criteria, data was missing in more than 50% of cases; temperature dysregulation in up to 63.3%, behavioral in up to 75.0%, and sleep disorders in up to 46.7%.

Discussion

We propose to use a uniform novel scoring system for hypothalamic dysfunction. Systematic scoring signs and symptoms that may be caused by hypothalamic dysfunction may help to early recognize hypothalamic dysfunction in patients at risk.² Signs and symptoms of hypothalamic dysfunction may be subtle and not always mentioned by the patient or its parents. Also, when not specifically asked for by the treating physician, signs and symptoms of hypothalamic dysfunction may be overlooked as is illustrated by the high number of missing data in our retrospective cohort analysis. In addition, the score may aid in understanding the etiology of presenting symptoms, help to predict its course and improve its management. Also, to have a scoring system for hypothalamic dysfunction may be useful for research purposes as outcomes of different cohorts can be better compared when the same criteria are used. We envision that in future cohort studies and registries, this novel hypothalamic score will be used.

We tested the score for feasibility in our retrospective cohorts and found HS to be present in 52.5% of patients. Presence of objective criteria such as (pan-) hypopituitarism with DI and adipsia was found in 3.3%–6.7% and severe overweight in 23.3%–35.0% of patients.

As is given in Table 3, however, missing data was present for some criteria in up to 63.3% (eg, for presence of temperature dysregulation). This illustrates that in current medical practice, even in patients known with symptoms of hypothalamic dysfunction such as with severe weight gain or obesity, other signs and symptoms of hypothalamic dysfunction are not always registered and it may be questioned whether these have been questioned or monitored. Awareness of the different aspects of hypothalamic dysfunction, such as hypothermia, may be increased by the introduction of our hypothalamic score. This awareness may, subsequently, help to improve patient care and outcome for instance by improving core body temperature which will positively impact complaints of fatigue and improve metabolism. Furthermore, it can draw attention to clues of endocrine (hypothalamic) problems for specialist such as oncologists and thereby result in more early referral to an endocrinologist.

The novel score thus seems feasible, however it was only checked in 120 patients and in retrospective cohorts. For this reason, the score must first be applied in future studies in order to draw more definite conclusions on prevalence of HS in patients at risk. In addition, the percentages of hypothalamic signs/symptoms and hypothalamic score may be expected to increase if in prospective cohorts the signs and symptoms of hypothalamic syndrome are systematically screened by validated questionnaires.

To give an idea of the sensitivity and specificity of the diagnostic criteria for hypothalamic dysfunction, it would also be

nice to apply and compare the hypothalamic score in patients with suprasellar tumors to a control population with another disease. Due to the retrospective design and the unavailability of a control population with also radiological data available, such a comparison could currently not be made, but this may be done in future studies.

The variables in the proposed diagnostic score were chosen based on literature of the HS in combination with the six clinical domains that were proposed to use for characterization of the patient suspect for hypothalamic dysfunction by van Iersel et al (ie, psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia, and hypopituitarism).^{2,15} By characterizing the patients according to these clinical domains, treatment can be made more individualized using the algorithm for hypothalamic dysfunction with a stepwise approach for each clinical domain. We believe that this clinical characterization may not only be useful for treatment, but that, by the introduction of this scoring system using similar clinical signs and symptoms, also early recognition of presence of hypothalamic dysfunction will be improved, including awareness of all the different aspects of this rare syndrome in patients who are already known with hypothalamic dysfunction.

As is elaborated on in the “Results” section, we have chosen to characterize signs and symptoms of hypothalamic dysfunction for some categories in a way that is “easy to apply” with available clinical data, eg, by subdividing a score into 0 (not present), 1 (mild), 2 (severe), and for other categories more specific, such as the Epworth Scale or the Hyperphagia Questionnaire. In this way, we aim to enable the score not only to be used in prospective cohorts, but also in retrospective cohorts. When the score is used for future reporting of prevalence numbers, it will be important to state how the score has been determined. For the evaluation of behavioral problems, available neuropsychological investigation data may be used as a surrogate for hypothalamic dysfunction-related behavioral problems.

Conclusion

We propose a novel scoring system for signs and symptoms of hypothalamic dysfunction in pediatric cohorts as well as new diagnostic criteria for the presence of the HS, using clinical, radiological, and pre-likelihood criteria. This score was tested and considered feasible. Hopefully, with this system and these criteria, earlier recognition of hypothalamic dysfunction and more uniform outcome measures to compare and report prevalence of HS in research are provided. Further prospective studies on clinical feasibility of this scoring system are warranted.

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