

RESEARCH

Resting energy expenditure in children at risk of hypothalamic dysfunction

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Abstract

Objective: Children with suprasellar brain damage are at risk of hypothalamic dysfunction (HD). HD may lead to decreased resting energy expenditure (REE). Decreased REE, however, is not present in all children with HD. Our aim was to assess which children suspect for HD have low REE, and its association with clinical severity of HD or radiological hypothalamic damage.

Patients and methods: A retrospective cohort study was performed. Measured REE (mREE) of children at risk of HD was compared to predicted REE (pREE). Low REE was defined as mREE <90% of predicted. The mREE/pREE quotient was associated to a clinical score for HD symptoms and to radiological hypothalamic damage.

Results: In total, 67 children at risk of HD (96% brain tumor diagnosis) with a mean BMI SDS of $+2.3 \pm 1.0$ were included. Of these, 45 (67.2%) had low mREE. Children with severe HD had a significant lower mean mREE/pREE quotient compared to children with no, mild, or moderate HD. Mean mREE/pREE quotient of children with posterior hypothalamic damage was significantly lower compared to children with no or anterior damage. Tumor progression or tumor recurrence, severe clinical HD, and panhypopituitarism with diabetes insipidus (DI) were significant risk factors for reduced REE.

Conclusion: REE may be lowered in children with hypothalamic damage and is associated to the degree of clinical HD. REE is, however, not lowered in all children suspect for HD. For children with mild or moderate clinical HD symptoms, REE measurements may be useful to distinguish between those who may benefit from obesity treatment that increases REE from those who would be better helped using other obesity interventions.

Key Words

- ▶ hypothalamic obesity
- ▶ suprasellar tumor
- ▶ resting energy expenditure
- ▶ posterior hypothalamic damage

Endocrine Connections
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Introduction

Hypothalamic dysfunction (HD) during childhood may be present in children with craniopharyngioma, chiasmatic hypothalamic glioma, germinoma, as well as in children with certain genetic syndromes, such as Prader Willi syndrome (1, 2, 3, 4, 5).

Due to the fact that the hypothalamus plays an essential role in endocrine balance, nutritional habits, and body composition, HD may lead to hypothalamic obesity (HO) (5, 6). In children with acquired brain damage, however, many other factors may induce weight gain, such as impaired mobility, visual impairment, disrupted sleep, use of medication, and poor adherence to dietary

or physical activity guidelines (5, 7, 8, 9, 10, 11). To enable adequate counseling, it is important to distinguish HD from other causes of weight gain.

Hypothalamic weight gain is caused by a disturbance of the essential parts of the hypothalamus: the ventromedial hypothalamus (VMH), paraventricular nuclei (PVN), arcuate nucleus (ARC), the lateral hypothalamic area, and posterior hypothalamic area (12). Disinhibition of vagal tone due to damage to the paraventricular nucleus (sympathetic) and suprachiasmatic nucleus (SCN) (parasympathetic) negatively influences lipogenesis and beta cell secretion of insulin, resulting in hyperinsulinism and fat storage. Damage to the ventromedial nucleus causes loss of satiety through the inability to integrate afferent hormonal signals including leptin, insulin, and gut hormones like GLP-1. Additionally, the disruption of autonomic function damages the biologic clock and therefore the circadian activity (13). Next to energy balance, the hypothalamus also plays an essential role in the body's temperature regulation, thirst sensation, and pituitary regulation (5).

In children with HD, hyperphagia was long thought to be the major cause of HO. However, hyperphagia is not present in all children with HO, and recent studies suggest that hyperphagia is significant risk factor but not a requisite for the development of HO (14, 15, 16). Changes in energy expenditure have been hypothesized to play a major role in weight gain and development of HO. Resting energy expenditure (REE) is the energy expenditure of the basic physiological functions necessary to maintain homeostasis in the human body (17). A decreased REE, not associated with differences in terms of body composition, was shown to be present in patients with CP compared with controls (18). In addition, lower energy intake/REE ratios were associated with third ventricle involvement of CP (15).

The severity and consequence of HD during childhood may be different, despite surviving the same tumor type in the hypothalamic region, and the degree of HD can be hard to predict. The differences in outcome of these children may be explained by damage to different hypothalamic nuclei, and it is uncertain in which children the REE is reduced (5).

For radiological scoring of hypothalamic damage, several MRI grading systems have been developed (19, 20). The degree of radiological damage is, however, not always related to the clinical degree of HD or to the presence of obesity. In the search for prevention and treatment of HO, additional tools are needed to better identify the cause of weight gain. In this light, measurement of REE may be an

interesting tool; when decreased REE is found, therapeutic interventions aiming to increase REE by stimulating sympathetic activity may be considered (21, 22, 23). Amphetamine treatment has been attempted in children with HO with good response in some, but not all, which may perhaps be explained by differences in REE (24, 25).

REE in children gaining weight with suspected hypothalamic damage has never been associated to radiological or clinical scores for hypothalamic damage. Our aim was to assess which children suspect for HD in our clinic had low REE and if outcomes of REE measurements could be associated to clinical severity of HD or to radiological posterior hypothalamic damage.

Methods

Study population

A retrospective study was performed in children (age > 3 years) referred to the department of pediatric endocrinology at risk of HD due to underlying etiology. All patients had undergone REE measurement (routine part of the clinical assessment in our outpatient clinic to calculate dietary caloric advice), using indirect calorimetry from the period 2014 to 2020.

In all children, REE was measured between 08:00 and 10:00 h in thermoneutral conditions using the Cosmed Quark RMR (Cosmed, Rome, Italy), Geratherm Ergostik (Geratherm Respiratory GmbH, Ergostik, Geratherm, Germany), or Q-NRG devices (Cosmed) (26, 27, 28, 29). With these devices, exhaled gas was captured by a canopy (ventilated hood system) or a face mask connected to oxygen and carbon dioxide analyzers mounted on a metabolic cart. The subjects were in the fasting state for at least 8 h, that is, from at least 00:00 h, were asked to refrain as much as possible from (intense) physical activity for the last 8 h and had been waiting for at least 30 min in the sitting position before REE measurement. Respiratory gas exchanges were monitored for 30 min. Steady-state ventilation of at least 5 min was defined as an average minute VO₂ and VCO₂ changes by <10% and the average RQ changes by <5%. The Weir equation was used to calculate REE (30).

Technical specifications of the indirect calorimetry devices

Cosmed Quark RMR: O₂ sensor $\pm 0.1\%$ Vol, CO₂ $\pm 0.02\%$ Vol, and flow accuracy $\pm 2\%$ or 20 mL/s. In two studies, a reliable accuracy of this device was reported (26, 31).

Geratherm Ergostik: O₂ sensor $\pm 0.1\%$ Vol (13–21%), CO₂ $\pm 0.1\%$ Vol (2.5–7.5%), and flow accuracy $\pm 3\%$ or 50 mL/s. The Ergostik gas analyzer (Geratherm Respiratory) was reported to be a reliable device which can collect indirect calorimetry-related outcomes in both resting conditions (e.g. REE) and during exercise (e.g. maximal fat oxidation), having a good inter-day reliability (27). Q-NRG[®] indirect calorimeter (Cosmed Quark RMR): accuracy has been reported (*in vitro*) to be within 5% at oxygen enrichment to 70%; that is maximum expected for clinical use (32). The *in vitro* coefficient of variation was <1% for REE, this is well within the specifics maintained in the literature for metabolic analyzers. A very good accuracy and precision of the Q-NRG[®] indirect calorimeter have been reported (33).

In all patients, height, weight, tanner stage, and pituitary function had been measured. All cases with pituitary dysfunction were adequately treated. Because data were collected retrospectively, the local institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply and provided a waiver.

Data collection

Patient characteristics

Demographic and brain injury-related characteristics were extracted from medical records. Anthropometric data (weight SDS, height SDS, and BMI (SDS)) at moment of REE measurement were collected. Presence of underweight, overweight, or obesity was determined by using the BMI cut-off points per age defined by Cole *et al.* (34, 35).

REE measurements

For the main outcomes, for each patient, the predicted REE (pREE) was calculated using the Schofield equation based on age, gender, weight, and height (36). As absolute measured REE values (mREE) are dependent on these factors, a quotient of mREE and pREE was calculated (mREE/pREE). For comparison, pREE and mREE/pREE were also calculated using other equations (33, 37, 38, 39, 40, 41, 42, 43, 44, 45). The level of normal REE was set on $\geq 90\%$, based on the results of Chima *et al.*, who reported that the accuracy in all age groups varied with mean bias ranging from an underestimation of 14.0% to an overestimation of 11.6%, as when compared to measured values. Precision has been defined as calculated by the percentage of participants with predicted energy expenditure within 10% of measured values (32). For this reason, it was presumed that mREE/pREE < 90% is the starting point of clinical relevance.

Clinical score for hypothalamic dysfunction

Clinical presence of HD was scored by an adjusted clinical HD score (adapted from de Vile *et al.* (46)), rating HD as: (a) grade I (mild); presence of postoperative obesity (BMI > +2.0 SDS) or weight gain (>+1.5 BMI SDS) with no change in effect or behavior indicative of hypothalamic HD; (b) grade II (moderate); obesity (BMI >+2.0 SDS) or weight gain (>+1.5 BMI SDS) in addition to the presence of an obvious period of hyperphagia or an associated change in affective behavior or memory; and (c) grade III; presence of obesity (>+3.0 BMI SDS) or extreme weight gain (>+2.0 BMI SDS) with hyperphagia and presence of other signs of HD, such as impaired thirst, rage, or disturbances of thermoregulation, memory, or sleep-wake pattern (46).

Endocrine dysfunction score

Endocrine dysfunction was graded as 0 (no pituitary dysfunction present), grade I (partial anterior pituitary dysfunction and/or diabetes insipidus (DI)), grade II (panhypopituitarism with DI), and grade III (panhypopituitarism with DI and impaired thirst regulation) (46).

Neuroimaging

On the brain MRI performed at time of diagnosis, the following items were scored: location of brain tumor, tumor volume, presence of hydrocephalus, presence of the pituitary stalk, identification of the supra-optic recess, infundibular recess, and hypothalamic region (47). Hypothalamic damage was scored only in children with brain tumor diagnosis using an adjusted 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, that is involving the area beyond the mammillary bodies (Fig. 1) (20). Mammillary body involvement was separately scored as none, mild involvement (dislocation), or severe involvement (unrecognizable structures) (47). Tumor volume was calculated based on the maximal tumor diameters measured in three dimensions (volume = $a \times b \times c / 2$) and hydrocephalus was scored as present if has two or more of the following criteria: Evan's score >0.30, mamillopontine distance >5.5 mm, callosal angle <80°, or third ventricle width >3.5 mm were seen on MRI. All items were scored by a trained clinician-scientist. The MRI images of the first 20 patients were also scored

by a neuroradiologist (more than 20 years of experience) and compared. For the remaining MRI images, if there was uncertainty of the physician scientist, the scoring was evaluated with the neuroradiologist and consensus was reached by discussion. In the last available brain MRI before REE measurement, the following items were scored:

hypothalamic damage (only in children with brain tumor diagnosis) using an adjusted Muller grading consisting of grade 0: no hypothalamic lesion, grade I: hypothalamic lesion of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, grade II: hypothalamic lesion of the anterior and/or solely posterior

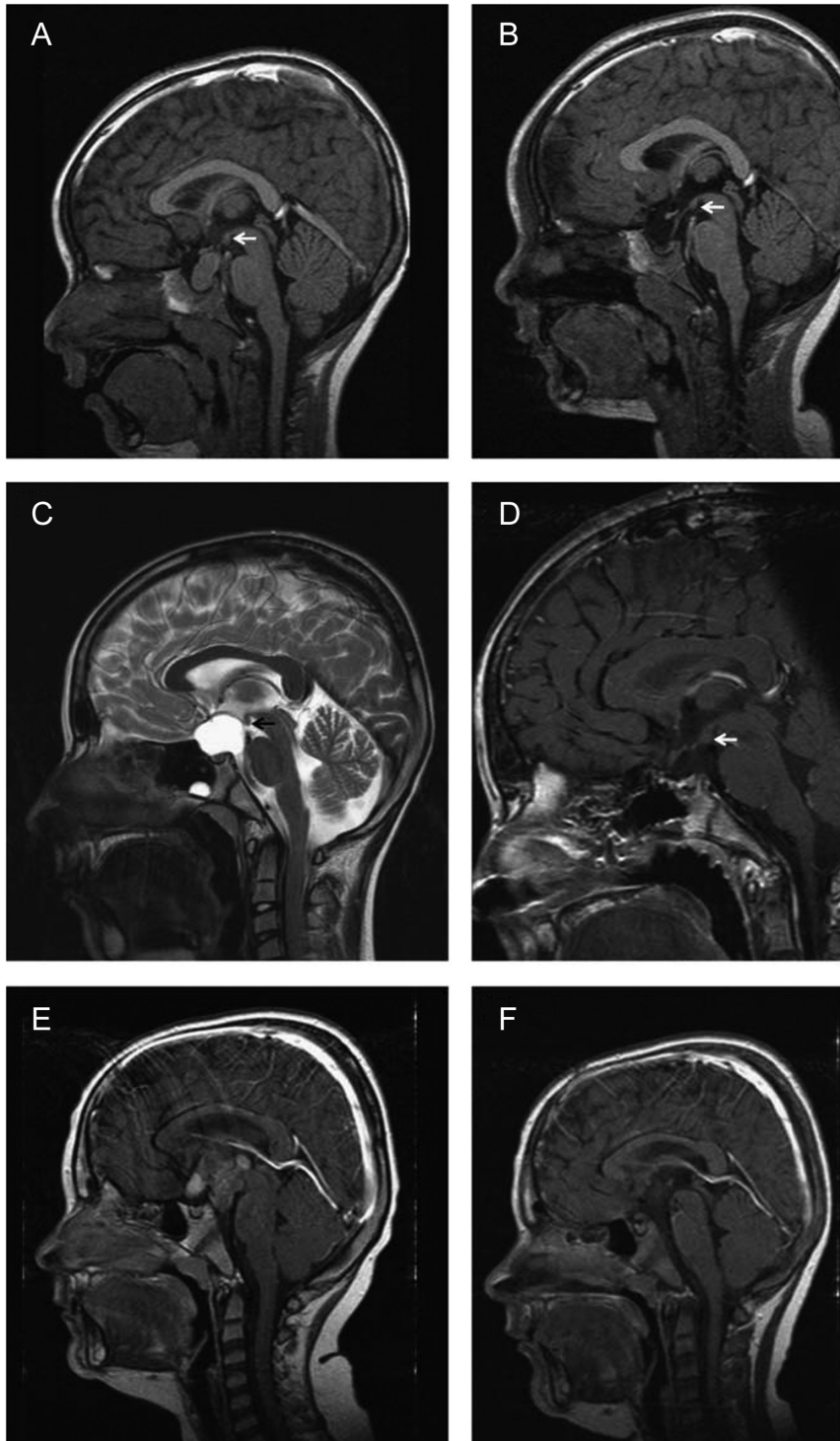


Figure 1

MRI imaging at diagnosis and 36 months after surgery in three cases of childhood craniopharyngioma with different grade of hypothalamic involvement/lesion. (A and B) Patient with craniopharyngioma confined to the intrasellar space (grade 0 = no hypothalamic involvement (A)/surgical lesion (B)). (C and D) Patient with craniopharyngioma involving the anterior hypothalamus (grade I: hypothalamic involvement (C)/surgical lesion of the anterior hypothalamic area (D)). (E and F) Patient with craniopharyngioma involving the anterior and posterior hypothalamus (grade II: hypothalamic involvement (E)/surgical lesion of the anterior and posterior hypothalamic area (F)). Arrows indicate mammillary bodies, defining the border between anterior and posterior involvement/lesion. Republished with permission of European Society of Endocrinology, from 'Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up', Müller *et al.*, vol 165 iss 1, 2011 (20). Permission conveyed through Copyright Clearance Centre, Inc.

hypothalamic area, that is involving the area beyond the mammillary bodies (20). Mammillary body damage was separately scored as none, mild damaged (one-sided), or severe damage (both sided) (47). All items were scored by a trained clinician-scientist and a second-blinded independent reviewer (neuroradiologist). The grading was compared and if there was a discrepancy, consensus was reached by discussion.

Statistical analysis

Data are presented as mean ± s.d. or median (range) for continuous data, depending on the distribution. Data are presented as percentages for categorical variables. Between-group differences were evaluated by Student's *t* test for continuous data with a normal distribution, Mann-Whitney *U* test for continuous data with a skewed distribution and by χ^2 test or Fisher's exact test for categorical data. To assess violation of normality distribution, QQ plot of the residuals and the Shapiro-Wilk's test were employed. Between-group differences were evaluated by one-way ANOVA for continuous data with a normal distribution, Kruskal-Wallis test for continuous data with a skewed distribution (skew variables were not further transformed), and by χ^2 test or Fisher's exact test for categorical data. *Post hoc* testing with Dunnett *t* (two-sided), with the last category as reference, was used. To study the effect of possible risk factors on the outcome, univariate and multivariable linear regression analysis was estimated. Independent variables to be included in the multivariable linear regression were selected by estimating first the univariate model and by considering the clinical relevance of each variable. A *P*-value of <0.05 was considered statistically significant. Analyses were performed by using SPSS version 25.0.

Results

Patient characteristics

Among the 67 children with suspected HD and weight gain or obesity, 38 (56.7%) were female. Mean age at brain injury diagnosis was 6.8 years ± 4.2 and mean age at follow-up (time of REE measurement) was 11.4 years ± 3.9. Mean BMI SDS at REE measurement was 2.3 ± 1.0, and mean delta BMI SDS from diagnosis to moment of REE measurement was 2.2 ± 1.98 (*n* = 51). In total, 63 (94.0%) children had been diagnosed with a brain tumor, 1 child had brain trauma, 1 brain infection, 1 congenital brain malformation, and 1 a Rathke's cleft cyst (Table 1).

REE

In total, REE was measured in 9 children (13.4%) with the device Cosmed Quark RMR (Cosmed), in 46 children (68.7%) with Geratherm Ergostik (Geratherm Respiratory GmbH), and in 12 children (17.9%) with the device Q-NRG. In the nine children, who had REE measurement with the device Cosmed Quark RMR (Cosmed), two (22.2%) were measured in 2014, three (33.3%) in 2015, one (11%) in 2016, and three in 2019 (33.3%). Of the 46 children measured with device 107 Cosmed Quark RMR, 9 (19.6%) were measured in 2018 and 37 (80.4%) were measured in 2019. All 12 children (100%) who were measured with the device Q-NRG were measured in 2020. Of the 67 children, mean mREE/pREE quotient computed using the Schofield equation was 0.83 ± 0.18 (range, 0.33–1.27). In total, 45 children (67.2%) had a mREE < 90% of the predicted

Table 1 Patient characteristics.

	Total group (<i>n</i> , %) (<i>n</i> = 67,100)
Female/male	38 (56.7)/29 (43.3)
Mean age at diagnosis (years)	6.8 ± 4.2
Mean age at REE measurement (years)	11.4 ± 3.9
Mean weight SDS at follow-up	1.8 ± 1.4
Mean height SDS at follow-up	−0.46 ± 1.3
Mean BMI SDS at diagnosis (<i>n</i> = 51)	0.06 ± 2.0
Mean BMI SDS at follow-up	2.3 ± 1.0
Weight classification at follow-up	
Normal weight	16 (23.9)
Overweight	24 (35.8)
Obesity	27 (40.3)
Mean fat mass % (<i>n</i> = 54)	32.5 ± 9.5
Primary diagnosis	
Craniopharyngioma	28 (41.8)
Low-grade glioma	28 (41.8)
(Mixed) germ cell tumor	5 (7.5)
Pineoblastoma	1 (1.5)
Unknown histology	1 (1.5)
Others**	4 (6.0)
Hydrocephalus	34 (50.7)
Mean tumor volume cm ³ (<i>n</i> = 63)	29.8 ± 41.7 (min 0.16–max. 236.5)
Treatment	
Neurosurgery	50 (74.6)
Radiotherapy, mean Gray ± SDS	23 (34.3), 48.0 ± 11.6
Chemotherapy	26 (38.8)
Intracystic interferon	6 (9.0)

Numbers are displayed as *n* (%) or mean ± standard deviation score.

**Rathke's cleft cyst, trauma, infection, Chiari I malformation.

REE, resting energy expenditure; SDS, standard deviation score.

value. Children with low mREE had more often surgical treatment (84.4% vs 54.5%, $P=0.008$), and there were more recurrences in the low mREE group (69.8% vs 40.0%, $P=0.025$).

Clinical presence of hypothalamic dysfunction and REE outcomes

Using the adjusted HD criteria of de Ville *et al.* (46), 16.4% scored as having no HD, 31.3% as mild HD, 34.3% as moderate HD, and 17.9% as severe HD. The children with severe HD had a significant lower mean mREE/pREE quotient compared to children with no, mild, or moderate HD (severe: 0.65 ± 0.17 vs none: 0.89 ± 0.12 ($P=0.003$), mild: 0.86 ± 0.19 ($P=0.002$), and moderate: 0.88 ± 0.15 , ($P < 0.001$)). These outcomes were similar if pREE was calculated with other equations (Supplementary Table 1, see section on [supplementary materials](#) given at the end of this article).

In 45.5, 38.1, and 39.1% of children with no, mild, or moderate HD, respectively, the percentage of mREE/pREE was $\geq 90\%$ of predicted REE. In none of the children with severe HD ($n=12$), the percentage of mREE/pREE was $\geq 90\%$.

Endocrine dysfunction

In 76.1%, one or more pituitary deficiencies had been diagnosed, of which 23.9% had an endocrine dysfunction score grade I (partial anterior deficiency and/or DI), 46.3% grade II (panhypopituitarism and DI with adequate thirst feeling), and 6.0% grade III (panhypopituitarism and DI without adequate thirst feeling).

The mean mREE/pREE quotient was significantly lower in children with grade III endocrine dysfunction compared to children with grade I or II endocrine dysfunction (mean mREE/pREE quotient of 0.58 ± 0.14 vs children with grade 0: 0.88 ± 0.11 ($P=0.006$), grade I: 0.88 ± 0.16 ($P=0.006$), and grade II: 0.82 ± 0.20 , ($P=0.023$)). These outcomes were similar when pREE was calculated with other equations, except for comparison of grade II endocrine dysfunction with grade III endocrine dysfunction. Two of the in total 12 equations did not find a significant difference (Mifflin $P=0.124$ and Schmelze $P=0.077$).

Radiological assessment of hypothalamic damage

MR images at time of diagnosis were available for 61 children with a brain tumor. The mean mREE/pREE quotient of children at time of diagnosis did not differ

between Muller grade 0 (0.89 ± 0.11), I (0.88 ± 0.15), and II (0.78 ± 0.20) ($P=0.087$). These outcomes were similar when pREE was calculated with other equations (Table 2).

At time of REE measurement, MR images were available for 62 children with a brain tumor. The mean mREE/pREE quotient of children with Muller grade II on MRI at time of REE measurement ($n=34$) was significantly lower compared to children with grade 0 or grade I hypothalamic damage (mean REE quotient in patients with Muller grade II: 0.77 ± 0.19 vs grade 0: 0.89 ± 0.09 and grade I: 0.90 ± 0.16 , $P=0.017$). These outcomes were similar when calculated with other equations. Four equations (Harris and Benedict, Mifflin, Muller, and Schmelze) did not show a statistically significant difference (Supplementary Table 2).

The mean mREE/pREE quotient of children with severe mammillary body damage on MRI at time of REE measurement was significantly lower compared to children with no mammillary body damage or mild damage on MRI (no damage 0.88 ± 0.10 , mild damage 0.86 ± 0.18 , severe: 0.74 ± 0.18 , $P=0.016$). These outcomes were similar using nine other equations, and two equations (Harris and Benedict $P=0.067$ and Mifflin $P=0.136$) did not find a statistically significant result.

Clinical HD in relation to radiological score

All children with severe clinical HD scores scored Muller grade II on the MRI at diagnosis and 11 of 12 scored Muller grade II on the MRI at time of REE measurement. Among children with posterior hypothalamic damage (grade II) ($n=34$), 3 (8.8%) had no clinical HD (grade 0), 11 (32.4%) had mild HD (grade I), 9 (26.5%) moderate HD (grade II), and 11 (32.4%) severe HD (grade III) (Fig. 2).

Risk factors for mREE/pREE quotient

In the multivariable linear regression, progression or recurrence of the tumor, severe clinical HD, and panhypopituitarism with DI were found to be statistically significant risk factors to develop lower mREE/pREE quotient (mREE/pREE quotient = $0.99 + -0.09$ (1 = tumor progression or recurrence) + -0.12 (1 = severe clinical hypothalamic dysfunction) + -0.09 (1 = panhypopituitarism with DI) (Tables 3 and 4).

Discussion

In this study, we aimed to assess which children, presenting with weight gain or obesity, suspect for HD have lower REE

Table 2 MRI characteristics and resting energy expenditure quotient.

	Mean mREE/pREE quotient ^a ± SDS	P-value
MRI characteristics at time of primary diagnosis (<i>n</i> = 65):		
Pituitary stalk identification		0.144
Present (<i>n</i> = 26)	0.86 ± 0.13	
Absent (<i>n</i> = 39)	0.80 ± 0.20	
Hypothalamic identification		0.019*
Present (<i>n</i> = 31)	0.88 ± 0.13	
Absent (<i>n</i> = 34)	0.78 ± 0.20	
Hydrocephalus ^b		0.582
Present (<i>n</i> = 31)	0.82 ± 0.19	
Absent (<i>n</i> = 34)	0.84 ± 0.16	
Muller grading for presence of hypothalamic damage ^c (<i>n</i> = 61)		0.087
None (<i>n</i> = 7)	0.89 ± 0.11	
Anterior damage (<i>n</i> = 20)	0.88 ± 0.15	
Posterior damage (<i>n</i> = 34)	0.78 ± 0.20	
Mammillary body involvement ^d		0.128
No involvement (<i>n</i> = 25)	0.88 ± 0.10	
Mild involvement (<i>n</i> = 13)	0.77 ± 0.22	
Severe involvement (<i>n</i> = 27)	0.81 ± 0.20	
At time of REE measurement (<i>n</i> = 66):		
Hypothalamic damage according to Muller grading ^c (<i>n</i> = 62)		0.017*
None (<i>n</i> = 10)	0.89 ± 0.09	
Anterior damage (<i>n</i> = 18)	0.90 ± 0.16	
Posterior damage (<i>n</i> = 34)	0.77 ± 0.19	
Mammillary body damage ^d		0.023*
No damage (<i>n</i> = 17)	0.88 ± 0.10	
Mild damaged (<i>n</i> = 29)	0.86 ± 0.18	
Severe damaged (<i>n</i> = 20)	0.74 ± 0.18	

^amREE/REE quotient: measured resting energy expenditure divided by predicted resting energy expenditure (calculated by Schofield equation).

^bHydrocephalus was scored as present if has two or more of the following criteria: Evan's score >0.30, mamillopontine distance >5.5 mm, callosal angle <80°, or third ventricle width >3.5 mm were seen on MRI. ^cHypothalamic damage was scored only in children with brain tumor diagnosis, using an adjusted Muller grading consisting of grade 0: no hypothalamic involvement/lesion, grade I: hypothalamic involvement/lesion of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, and grade II: hypothalamic involvement/lesion of the anterior and/or solely posterior hypothalamic area, i.e. involving the area beyond the mammillary bodies. ^dMammillary body damage was separately scored as none, mild involvement or damage (dislocation or one-sided damage), or severe involvement or damage (both sided damaged or unrecognizable structures). REE, resting energy expenditure. *Statistically significant.

and if this is associated with other clinical signs of HD or radiological damage. To have this information may aid in the management of HO, as it will distinguish those with lower REE that may be helped by treatment with energy expenditure increasing interventions, from those that do not and may need other obesity interventions.

In this cohort, we could relate REE measurement outcomes to clinical severity of HD and radiological posterior hypothalamic damage. However, our results also demonstrate that some children who are clinically or radiologically suspect for HD have REE measurement outcomes comparable to age and gender-related predicted values. This emphasizes an important message that underlies the difficult problem of HO; not in all children with hypothalamic damage, the etiology of weight gain is the same. To better understand the individual etiology of weight gain, measurement of REE may be useful to design adequate personalized coaching and treatment.

It may be objected that obesity itself may be associated with a lower REE due to the presence of a higher percentage of fat mass with decreased muscle mass. Obesity, however, does not lower absolute REE, but results in an increased absolute REE (48). When body composition (fat-free mass) is considered, the differences between obese and non-obese individuals disappear, which implicates that REE in obese individuals is not different from healthy subjects (48).

Clinical and radiological HD scores can be difficult to interpret, and a one-to-one correlation between anatomical damage and clinical outcome is difficult to test. For example, a child with posterior hypothalamic damage (grade II) does not necessarily have decreased REE or a high clinical HD score. To our knowledge, this is the first study in which REE measurements of children with brain injury at risk of HD have been associated with scores for clinical HD and radiological hypothalamic damage. Previous cohort studies have examined REE measurements in children with brain

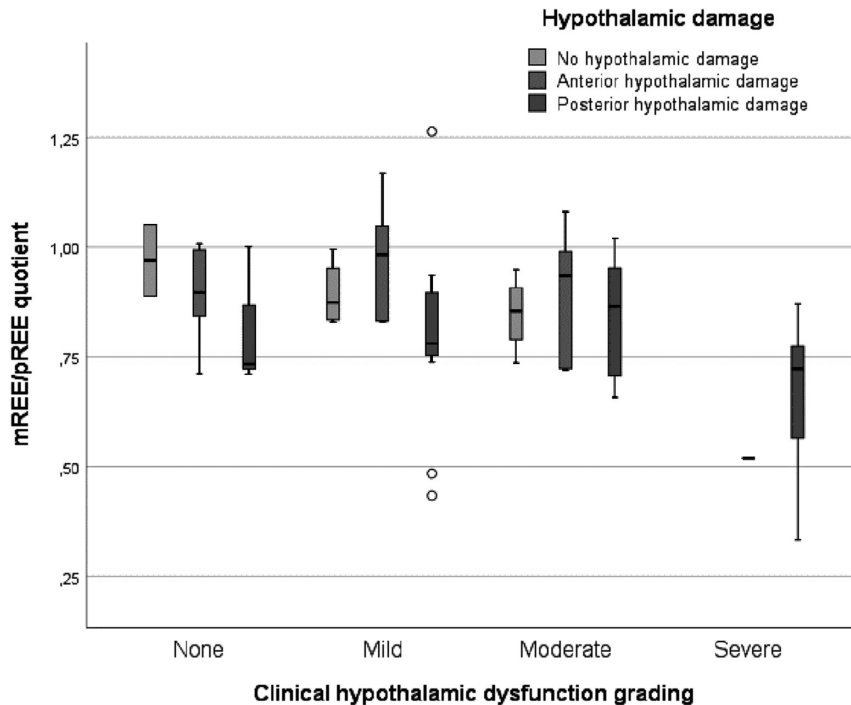


Figure 2 Clustered boxplot of resting energy expenditure quotients of children. Resting energy expenditure quotient: measured resting energy expenditure (mREE) divided by predicted resting energy expenditure (pREE) (calculated by Schofield equation).

injury and compared them to obese children without brain injury or compared REE measurements in normal weight craniopharyngioma (CP) patients with those in obese CP patients (15, 18, 49, 50, 51, 52). REE was shown to be lower in CP patients compared to children with multifactorial obesity regardless of the amount of fat-free mass or when compared to matched controls (18). In another study, CP patients were shown to have a 17% lower REE value compared to the values that were expected from the WHO equation (49). Our study results confirm that REE may be

lowered in children with hypothalamic damage and shows that this is associated to the degree of clinical HD (in the multivariate analysis), as well as to radiological posterior hypothalamic damage (in the univariate analysis). The fact that posterior hypothalamic damage was not significant in the multivariate analysis may be explained by the fact that the current used radiological score grading anterior or posterior hypothalamic damage, even including mammillary body damage, is still too robust to predict the outcomes of REE. In addition, this grading system

Table 3 Univariate linear regression for resting energy expenditure quotient.

	Standardized beta	95% CI		P-value
		Lower	Upper	
Partial or gross total resection	-0.12	-0.21	-0.02	0.022*
Progression or recurrence of the tumor	-0.10	-0.19	-0.01	0.030*
Severe clinical hypothalamic dysfunction ^a	-0.23	-0.33	-0.12	<0.001*
Posterior hypothalamic damage ^b at time of diagnosis	-0.10	-0.19	-0.01	0.027*
Posterior hypothalamic damage on MRI at time of REE measurement	-0.13	-0.21	-0.04	0.004*
Severe mammillary body damage ^c	-0.12	-0.21	-0.04	0.007*
Pan hypopituitarism with diabetes insipidus	-0.9	-0.17	-0.00	0.050*

Resting energy expenditure quotient: Measured resting energy expenditure divided by predicted resting energy expenditure (calculated by Schofield equation). Diabetes insipidus at follow-up, central precocious puberty at follow-up, age at diagnosis, age at follow-up, BMI SDS at follow-up, fat-mass percentage ($n = 54$), hydrocephalus at diagnosis, tumor size ($n = 63$), severe mammillary body damage at diagnosis ($n = 65$), radiotherapy, and chemotherapy were not significantly associated with mREE/pREE quotient.

^aSevere clinical hypothalamic dysfunction: Presence of obesity ($>+3.0$ BMI SDS) or extreme weight gain ($>+2.0$ BMI SDS) with (severe) hyperphagia and presence of other clinical manifestations, such as impaired thirst, rage behavior, or disturbances of thermoregulation, memory, and sleep-wake pattern.

^bPosterior hypothalamic damage graded with Muller: hypothalamic involvement/lesion of the anterior and/or solely posterior hypothalamic area, i.e. involving the area beyond mammillary bodies. ^cSevere mammillary body damage: severe involvement or damage (unrecognizable structures or both sided damaged) of the mammillary bodies. *Statistically significant.

Table 4 Multivariate linear regression for resting energy expenditure quotient.

	Standardized beta	95% CI		P-value
		Lower	Upper	
Progression or recurrence of the tumor	-0.09	-0.17	-0.002	0.046*
Severe clinical hypothalamic dysfunction ^a	-0.12	-0.23	-0.012	0.030*
Posterior hypothalamic damage ^b on MRI at time of REE measurement	-0.05	-0.16	0.048	0.293
Severe mammillary body damage ^c	-0.03	-0.14	0.073	0.546
Pan hypopituitarism with diabetes insipidus	-0.09	-0.18	-0.009	0.030*

Resting energy expenditure quotient: Measured resting energy expenditure divided by predicted resting energy expenditure (calculated by Schofield equation).

^aSevere clinical hypothalamic dysfunction: Presence of obesity (>+3.0 BMI SDS) or extreme weight gain (>+2.0 BMI SDS) with (severe) hyperphagia and presence of other clinical manifestations, such as impaired thirst, rage behavior, or disturbances of thermoregulation, memory, and sleep-wake pattern.

^bPosterior hypothalamic damage graded with Muller: hypothalamic involvement/lesion of the anterior and/or solely posterior hypothalamic area, i.e. involving the area beyond mammillary bodies. ^cSevere mammillary body damage: severe involvement or damage (unrecognizable structures or both sided damaged) of the mammillary bodies. *Statistically significant.

was developed for craniopharyngioma patients, and in our study also other suprasellar tumors were included (e.g. germinoma, low grade glioma). Perhaps, the Muller grading system is not optimal for grading hypothalamic damage in such a heterogeneous group. Roth *et al.* developed a more detailed MRI scoring system for the risk assessment of HO and found posterior damage and mammillary body damage to be related to HO in mainly CP patients (53). In addition, Perez *et al.* evaluated the effect of glucagon-like-1 peptide receptor (GLP-1) agonist treatment in CP patients in relation to the degree of hypothalamic and MB damage, using this scoring system. They found that CP patients with a worse hypothalamic damage score, bilateral MB damage, or smaller MB in the cross-sectional area had a greater reduction in % body fat following GLP-1 agonist treatment (54). However, both studies did not associate HO or MRI score to REE outcomes and, therefore, no conclusion can be drawn on the exact underlying etiology of HO in these patients (hyperphagia or decreased REE or both). Perhaps, measuring the volume of the hypothalamic area may aid in predicting REE outcomes, as studies have shown that body weight was negatively associated to hypothalamic volume in patients with hypothalamic dysfunction (55). Furthermore, Fjalldal *et al.* found HT volume to be negatively correlated to fat mass and leptin among CP patients (56). It would, therefore, be of interest to correlate HT volume to REE outcomes as well. We suggest that future research takes REE measurements into account in relation to hypothalamic damage, which may aid to guide therapy and evaluate the effect of obesity therapy in these patients. Along with this, future research should focus on improving radiological techniques for detailed information on damage to the different nuclei of the hypothalamus, such as the arcuate nucleus, paraventricular nucleus, and dorsomedial nucleus.

In our cohort, all children with severe clinical hypothalamic dysfunction had a low REE (<90%). It could, therefore, be argued that REE measurement in these children may not be necessary anymore. However, REE measurement may be valuable for clinicians as a baseline value, which can be used for evaluation after interventions aiming to improve obesity. In addition, also dietary advice may be adjusted to REE values.

As discussed above, in the univariate analysis, we found an association between posterior hypothalamic damage with the Muller grading, mammillary body damage, endocrine dysfunction and clinical hypothalamic dysfunction, and low REE. However, in the multivariable linear regression, only tumor recurrence or progression, severe clinical hypothalamic dysfunction, and panhypopituitarism with diabetes insipidus were significant. We also found that not all children suspect for HD have a low REE, implying that measuring REE may aid in gaining more information on the etiology of weight gain in these patients and aid in designing individualized treatment programs targeting the right factors which contributed to weight gain in these patients. HO in hypothalamic patients is not one size fits all, some patients may have hyperphagia and some may have decreased REE, while again others have both. REE is thus one of the parameters, next to radiological scoring and clinical scoring in proving an holistic view of the patient. This is supported by our results, showing that almost all children without clinical signs have normal REE values and all children with severe clinical HD have low REE values. However, grading mild or moderate clinical HD does not discriminate between those children with normal REE and those with a low REE. This group is thus very heterogeneous, and measuring REE could be helpful for these children. New radiological techniques need to be developed which may be associated to the clinical picture and REE in the future.

For physicians treating children at risk of HD, it is important to understand the underlying etiology for the weight gain to enable appropriate counseling and treatment. It goes without saying that in all children, the first step for reducing weight gain is lifestyle intervention. However, when REE is lowered, lifestyle alone may not be sufficient to maintain or regain a healthy BMI and body composition (57, 58, 59, 60, 61). For these children, specific interventions aiming to increase REE, either by increasing physical activity, such as high intensity interval training or medical (e.g. dextroamphetamine) may be helpful (24, 25). Prescribing amphetamines must however be considered experimental and should only be done in experienced multidisciplinary setting. In addition, optimizing endocrine balance, such as aiming for FT4 concentrations in the upper range of the reference level, restoring the IGF-1 concentrations in children with growth hormone deficiency and aiming for low-normal hydrocortisone maintenance doses may aid to improve metabolic state (21, 22, 62).

Our selection of patients included in this cohort may be considered a limitation of this study. Children referred to the pediatric endocrinologist suspect for HD were included, which may have introduced a selection bias. Also, the retrospective design may be considered a limitation. Our results must therefore be confirmed in a prospective longitudinal study, using standardized questionnaires focusing on clinical HD, with comparison of outcomes to a control group.

Comparing mREE in individuals to predictive equations (pREE) is challenging, because all equations have their limitations. Multiple predictive equations exist, and no predictive equation is 100% valid for estimating the true REE of a child. If pREE is over-predicted, mREE/pREE may be misinterpreted as being too low. We used the Schofield equation based on a recent review that showed that the most accurate REE predictions (least biased) in obese children and adolescents were obtained using the Schofield equation (+0.8% (3–18 years); 0% (11–18 years); +1.1% (3–10 years)) (63). Because of the limitation of all predictive equations, we compared the outcomes using the Schofield equations with outcomes calculated by other predictive equations. These results were almost all similar, confirming the reliability of our results.

In conclusion, REE in children suspect for HD is mainly related to clinical severity of HD symptoms and is not always lowered. We recommend measurement of REE in such children, as it will help to develop a personalized approach for HD, aiming to improve cardio-metabolic health.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-22-0276>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Because data were collected retrospectively, the local institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply and provided a waiver.

Data availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Author contribution statement

J van Schaik contributed to the conception and design of the study, the analysis and interpretation of the study, drafted the first manuscript, and revised the manuscript critically. M Burghard, M Lequin, E A van Maren, A M van Dijk, T Takken, L Rehorst, B Bakker, L Meijer, E Hoving, A Y N Schouten-van Meeteren, M Fiocco, and W J E Tissing contributed to the analysis and interpretation of the work, drafted the manuscript, and revised the manuscript critically. H M van Santen contributed to the conception or design of the work, the acquisition, analysis and interpretation of the study, and revised the manuscript critically. All authors approve the final version to be published and agree to be accountable for all aspects of the work.

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