THERAPEUTIC ADVANCES in
Endocrinology and Metabolism

Original Research

Insights into body composition in pediatric craniopharyngioma patients after surgical treatment

Ther Adv Endocrinol Metab

2025, Vol. 16: 1–13

DOI: 10.1177/20420188251336087

Hussein Zaitoon, Ori Eyal, Michal Yackobovitch-Gavan, Ravit Regev, Yael Issan, Jonathan Roth, Shlomi Constantini, Yael Lebenthal and Avivit Brener

Abstract

Background: Craniopharyngioma, a benign suprasellar tumor, is typically treated surgically with radiotherapy when indicated. Due to its proximity to the pituitary-hypothalamic region, patients often experience endocrine deficiencies.

Objective: To explore the body composition components and their interaction with metabolic syndrome (MetS) components in pediatric craniopharyngioma patients after surgery.

Design: Longitudinal single-center real-life study of 33 pediatric patients who were diagnosed with craniopharyngioma for which they underwent surgery between 2012 and 2024.

Methods: Electronic medical reports were reviewed for clinical data, and a bioimpedance analysis (BIA) database was searched for body composition. Fifty-four BIA reports of 21 patients with craniopharyngioma were analyzed. The latest reported values were compared to those of 63 sex- and age-matched healthy controls. Changes in anthropometric measurements and indices of muscle and adiposity were assessed by linear mixed models.

Results: Patients with craniopharyngioma exhibited higher adiposity compared to controls, with significantly elevated total body fat percentage (FATP; $p < 0.001$), trunk-to-total body FATP ratio ($p = 0.012$), and lower muscle-to-fat ratio (MFR) z-scores ($p < 0.001$). The appendicular skeletal muscle mass (ASMM) z-scores were similar. A sex- and age-adjusted model revealed that the diagnosis of MetS components was positively associated with FATP [odds ratio = 1.13, confidence interval (1.04, 1.23), $p = 0.006$]. Patients with craniopharyngioma demonstrated an increase in ASMM z-score over time ($\beta = 0.14$, SE = 0.04, $p = 0.002$) together with a decline in sex- and age-adjusted FATP ($\beta = -0.99$, SE = 0.41, $p = 0.018$).

Conclusion: Despite struggling with obesity and hormonal deficiencies, survivors of craniopharyngioma showed favorable changes in body composition with appropriate medical interventions. Strategies to prevent metabolic complications and tailored hormone replacement therapies are essential for managing metabolic decline.

Correspondence to:
Avivit Brener
The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 6423906, Israel

Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
avivitb@tlvmc.gov.il

Hussein Zaitoon
Ori Eyal
Ravit Regev
Yael Lebenthal
The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

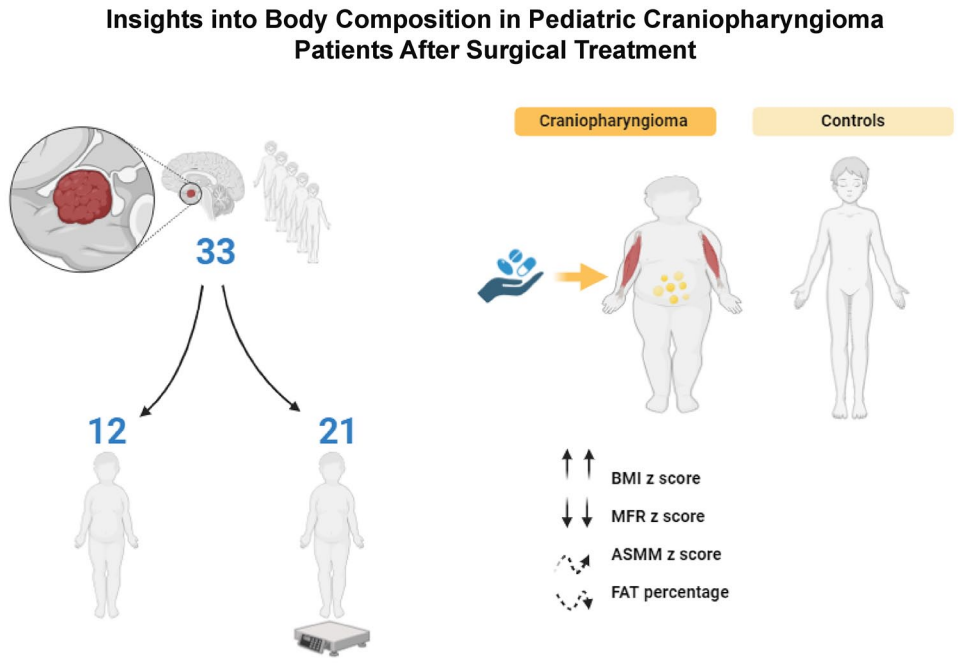
Michal Yackobovitch-Gavan
Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

Yael Issan
The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Jonathan Roth
Shlomi Constantini
Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

Department of Pediatric Neurosurgery, The Pediatric Brain Center, Dana-Dwek Children's Hospital, Tel Aviv Medical Center, Tel Aviv, Israel

Graphical abstract



Keywords: body composition, brain surgery, hormonal deficiency, metabolic syndrome, pediatric craniopharyngioma

Received: 8 July 2024; revised manuscript accepted: 1 April 2025.

Introduction

Craniopharyngiomas originate from remnants of the craniopharyngeal duct epithelium and comprise 1.2%–4.6% of all brain tumors.[1] They are the prevailing neoplasm within the suprasellar region, even though they comprise merely 5%–15% of intracranial neoplasms in children.[1]

Despite being considered benign, their location amidst vital structures, such as the pituitary gland and optic chiasm, poses a risk of a diverse range of severe clinical manifestations, such as hypothalamic obesity and various hormonal disturbances. Craniopharyngiomas diagnosed and treated in childhood demonstrate favorable survival rates, but most of the patients experience long-term sequelae attributable to various types and degrees of damage to the hypothalamic-pituitary region caused either by the tumor itself or by the various treatment modalities.[2] The potential correlation of this damage with a specific neurosurgical procedure poses a dilemma in choosing between a gross-total resection and limited resections followed by radiation when there is a risk of recurrence.[3]

Endocrine deficiencies are prevalent complications of craniopharyngiomas, having been reported to have profound implications for perioperative and long-term treatment outcomes.[4] The emergence of acute hormonal imbalance leading to an adrenal crisis and/or severe disruptions in fluid and electrolyte balance can even bear the potential for fatal outcomes. Chronic hormone deficits may result in abnormal growth and pubertal development in children as well as sexual dysfunction in adults, significantly lowering long-term quality of life.[5] Growth hormone deficiency (GHD) is the most common pituitary deficiency associated with craniopharyngiomas,

affecting 26%–75% of the patients at diagnosis and 70%–92% post-treatment[6,7] and exerting a substantial negative impact on longitudinal growth.[8] It also has a negative impact on body composition, as indicated by an increase in fat mass together with a reduction in lean body mass and bone mineral density.[9–11] Hypothyroidism may also result in lower muscle and bone mass combined with increased adiposity with truncal distribution. These negative effects have been observed to be reversible with thyroid hormone replacement therapy.[12] Adults with multiple hormonal deficiencies, particularly when hormone replacement therapy is inadequate, were reported to have exhibited increased fat mass and heightened risk for obesity, potentially contributing to metabolic syndrome (MetS) and cardiovascular morbidity.[13]

The body composition of pediatric craniopharyngioma survivors may be complicated, not only by multiple pituitary hormone deficiencies but also by hypothalamic dysfunction. Hypothalamic obesity in pediatric patients who have survived craniopharyngiomas represents one of the most severe consequences, often resulting in a postoperative increase in body weight of up to 55%, with a subsequent plateau observed in long-term follow-up.[14,15] The primary cause of hypothalamic obesity is damage to the ventromedial hypothalamus and arcuate nucleus, both of which are vital regulators of hunger, satiety, and energy balance.[16] There is reportedly a higher prevalence of MetS, ranging from 45% to 80% in childhood-onset craniopharyngioma.[17,18]

Body composition analysis, particularly that of body fat indexes, provides a means of evaluating both the quantity of body fat and the associated cardiometabolic risk.[19] This study investigated changes in body composition in children with craniopharyngiomas who underwent surgical and/or radiological treatment in combination with personalized hormonal therapy.

Materials and methods

Study design and participants

This real-life study included all pediatric patients with childhood-onset craniopharyngioma who were diagnosed and treated at the Pediatric Neurosurgery Department and were under the care of the Institute of Pediatric Endocrinology in Dana-Dwek Children's Hospital between January 2012 and January 2024. Excluded were patients who were diagnosed with pituitary-hypothalamic lesions other than craniopharyngioma. The diagnosis was based on neuroimaging and confirmed by pathology. All patients underwent evaluation of the pituitary hormonal axes at craniopharyngioma diagnosis and at each follow-up clinic visit, recommended every 4–6 months. Body composition assessment by bioimpedance analysis (BIA) has been incorporated into the routine evaluation in our pediatric endocrine clinic since 2018. This assessment is conducted in patients older than 5 years of age who are able to stand without support, with the goal of identifying and reducing modifiable cardiometabolic disease risk factors.[20]

The hospital's computerized data system was queried for pediatric patients with intracranial tumors, and those with the diagnosis of craniopharyngioma were reviewed for sociodemographic, surgical/radiologic, and clinical data. The institutional BIA database was searched to retrieve body composition assessments of patients diagnosed with craniopharyngioma to create a joint database. The BIA database was also searched for BIA assessment of sex- and age-matched healthy controls who were being followed for growth parameters.

Surgery

The neurosurgical care of patients in this study was provided by S.C. and J.R. Selecting the neurosurgical approach involves a nuanced and multifaceted decision-making process according to the extent and invasiveness of the required craniopharyngioma resection, taking into account the trade-off between complete surgical removal and the associated morbidity, and the high recurrence rates associated with limited surgery alone. The goals of the various surgical interventions undergone by the study participants included alleviating obstructive hydrocephalus, relieving local pressure on vital structures such as the optic apparatus, creating a safe distance from radiosensitive structures to facilitate postoperative radiation therapy, and attempting aggressive resection for potential cure in selected cases. The selection of a neurosurgical approach customized to each individual also considered clinical factors, such as the patient's age, tumor size, radiological features

(including cystic components), and anatomical properties. The surgical options included open craniotomy for resection, transsphenoidal resection or biopsy, and cyst drainage usually by means of a transventricular endoscopic approach and leaving a local catheter and an Ommaya reservoir for future cyst aspirations.

Radiotherapy

Postoperative radiotherapy is mostly considered in cases of subtotal resection or tumor recurrence. Over the years, the primary goal of surgery has shifted from attempting a gross-total resection to the alleviation of pressure on the optic apparatus and brainstem, followed by radiotherapy (usually proton-beam therapy).[3] Radiotherapy is, however, avoided in patients younger than 3 years of age due to heightened long-term side effects, such as neurocognitive decline.

Craniopharyngioma surveillance program

The study patients were followed by multidisciplinary surgical and medical teams that included neurosurgical, endocrine, neurological, and ophthalmologic professionals, as well as nutritional consultation and psychosocial guidance. Brain magnetic resonance imaging (MRI) was performed every 3–4 months during the first 2 postoperative years, every 6 months for the next 3 years, and annually thereafter in cases without evidence of recurrence. Those patients were also referred for laboratory evaluation of hormonal axes. Replacement therapy was prescribed for patients diagnosed as having a hormonal deficiency during follow-up. The multidisciplinary medical team includes nutritional consultation and psychosocial guidance.

Clinical characteristics and measurements

Medical records were reviewed to extract clinical information, including age at diagnosis, presenting symptoms, MRI findings at diagnosis, type of surgery, surgical complications, postoperative radiation therapy and dosage, pathological results, and clinical data documented at endocrine clinic visits (anthropometric and blood pressure (BP) measurements, body composition assessment, medical diagnoses and treatment, and imaging and laboratory evaluations). The anthropometric measurements that included height, weight, and body mass index (BMI, calculated as weight in kg divided by height in m^2) were standardized according to the CDC 2000 growth charts into sex- and age-specific standard deviation (SD) scores (z-scores).[21] Weight status categories were defined based on BMI z-scores as follows: underweight for BMI percentile $\leqslant$5th percentile (z-score $\leqslant -1.645$), overweight for BMI percentile $\geqslant$85th and $<$95th percentiles ($1.04 \leqslant z$-score < 1.645), and obesity for BMI percentile $\geqslant$95th percentile (z-score $\geqslant 1.645$).[22,23] Systolic and diastolic BP percentiles adjusted for sex, age, and height percentile were determined by means of an online age-based pediatric BP calculator.[24]

Body composition assessment by BIA for subjects aged 5 years and older was conducted with the Tanita Body Composition Analyzer (Tanita MC-780 MA) in combination with GMON Professional Software.[25] This method encompassed both whole-body and segmental assessments, targeting the trunk, upper limbs, and lower limbs to analyze fat and muscle distribution. The measurements took place during routine clinic visits between 8:00 am and 1:00 pm, with the subjects ideally in a fasting state and without recent strenuous physical activity. The report included data on fat percentage (FATP) and fat and muscle mass for the whole body, trunk, and limbs. The trunk-to-total body FATP ratio, appendicular skeletal muscle mass (ASMM, the sum of muscle mass of four limbs), and the muscle-to-fat ratio (MFR = ASMM in kg/fat mass in kg) were calculated. z-Scores for MFR and ASMM were calculated based on BIA pediatric reference curves.[26] The truncal-to-total body FATP was also recorded.

Laboratory evaluation for hormonal axes function included blood electrolyte levels, 8:00 am cortisol, thyroid function tests (thyroid-stimulating hormone and free thyroxin), insulin growth factor 1 (IGF1), gonadotropins, and sex hormones as indicated. IGF1 levels were converted to sex- and Tanner stage-appropriate z-scores according to normal reference ranges to allow standardization between individuals.

The definition chosen for childhood MetS components was as follows: glucose intolerance = fasting glucose $\geqslant$100 mg/dL (5.5 mM), elevated BP = systolic and/or diastolic BP $\geqslant$90th percentile for sex, age, and height,[27] hypertriglyceridemia = triglyceride (TG) levels $\geqslant$110 mg/dL (1.24 mM), and low high-density lipoprotein-cholesterol (HDL-c) = HDL-c $\leqslant$40 mg/dL (1.03 mM).

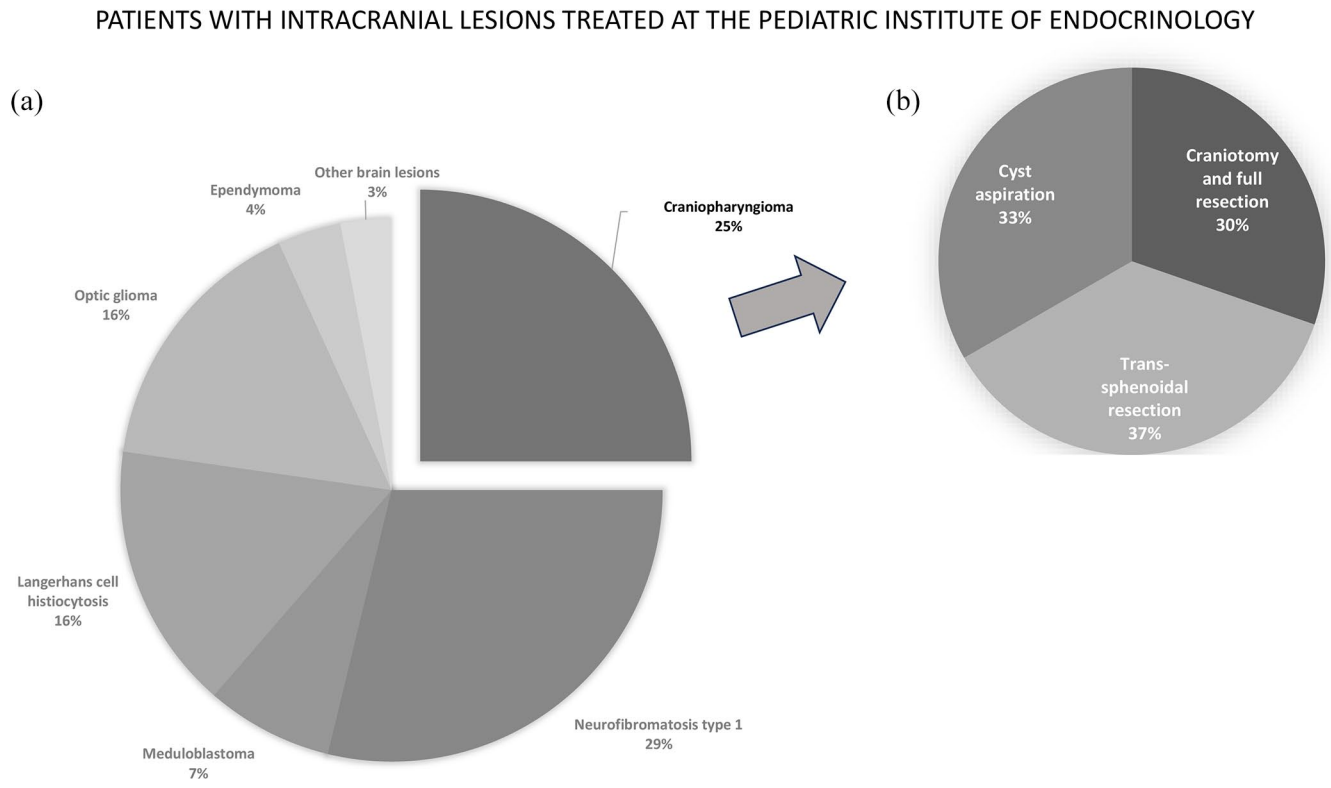


Figure 1. (a) The distribution of childhood-onset intracranial tumors diagnosed and treated at the Pediatric Neurosurgery Department and Institute of Pediatric Endocrinology during the study period. (b) The distribution of neurosurgical procedures employed in patients diagnosed with craniopharyngioma.

Control group

Healthy controls were defined as having normal stature (10th < height percentile < 90th) and normal timing of puberty and pubertal progression. Anthropometric measurements, body composition assessments by BIA, and BP measurements of healthy children and adolescents who were referred for growth evaluation to the Endocrine Institute were used for comparisons of growth parameters.

Statistical analysis

The data were analyzed using Statistical Package for the Social Sciences software version 29 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided. The data are expressed as means ± SDs for normally distributed variables and as median (interquartile range) for parameters with abnormal distribution. The independent samples Student's t test was used for comparing the means of variables. The Chi-square test (or Fisher's exact test for small count tables) was used to compare groups in categorical variables. Spearman correlations were applied to determine correlations between IGF-1 z-scores (skewed distribution) and anthropometric parameters and body composition components. Repeated measures linear mixed models were used to analyze inter-individual changes over time in BMI, MFR, and ASMM z-scores and FATP (with the FATP model adjusted for sex and age), accounting for variations in the number of follow-up visits and follow-up duration for each patient. Logistic regression models, adjusting for sex, age, socioeconomic position, and disease duration, were used to assess the association between body composition parameters (FATP, ASMM, and MFR z-scores) and the diagnosis of MetS components. A p value of $\leqslant 0.05$ was considered significant.

Results

During the study, 132 pediatric patients with intracranial tumors treated in the Pediatric Neurosurgery Department were referred for endocrine evaluation (Figure 1(a)). Craniopharyngioma was diagnosed in 33 patients (21 girls, 63.3%),

with a mean age of 12.0 ± 4.4 years (range 1.8–17.3). Nineteen presented with neurological symptoms, and 14 with endocrine symptoms (one presented with both). All of the 33 study patients underwent surgical procedures, with the choice of a neurosurgical approach based upon clinical considerations, such as age, tumor size, radiological characteristics (such as cystic components), and location. The distribution of their neurosurgical treatments was open craniotomy and full resection ($n = 10$, 30.3%), transsphenoidal resection ($n = 12$, 36.4%), and cyst aspiration ($n = 11$, 33.3%; Figure 1(b)). Nineteen patients (57.6%) underwent postoperative proton-beam radiotherapy administered at a standard dose of 54 Gy. Pathological examination identified adamantinomatous histology in all 33 cases, and none exhibited papillary histology.

During their endocrinologic follow-up (the duration of follow-up and the number of BIA assessments for each patient are presented in Supplemental Figure 1), 27 (81.8%) patients diagnosed with central hypothyroidism were treated with L-thyroxine, 18 (54.5%) with GHD initiated recombinant growth hormone (GH) therapy, 17 (51.5%) with adrenal insufficiency were treated with hydrocortisone, 16 (48.5%) with arginine-vasopressin deficiency were treated with desmopressin acetate, and 9 patients who reached a puberty-appropriate age (6 boys and 3 girls) diagnosed with sex hormonal deficiency received sex hormonal replacement therapy. Three patients did not have any hormonal deficiency, six had single hormone deficiency, while the rest had a variation of combined hormone deficiency (six had two hormonal deficiencies, eight had three hormonal deficiencies, five had four hormonal deficiencies, and five had five hormonal deficiencies).

Twenty-one patients with craniopharyngioma underwent repeated body composition assessments. Table 1 outlines the clinical characteristics and body composition parameters of those patients at their latest BIA assessment compared to 63 sex- and age-matched healthy controls. A comparison of the anthropometric measurements revealed significant differences between the patients with craniopharyngioma compared to controls, most notably lower height and weight z-scores ($p = 0.018$ and $p = 0.02$, respectively) and higher BMI z-scores ($p < 0.001$). Moreover, 11 children (52.4%) in the craniopharyngioma group were classified with obesity (five with obesity class 1 and six with obesity class 2–3) compared to only 3 (5%) children with obesity class 1 in the control group ($p < 0.001$).

The comparison of body composition components revealed higher adiposity indices of total body FATP, truncal FATP, and trunk-to-total body FATP ratio in patients with craniopharyngioma compared to controls ($p < 0.001$, $p < 0.001$, and $p = 0.012$, respectively). The mean MFR z-score of the patients with craniopharyngioma was significantly lower than that of the controls ($p < 0.001$), without any significant difference in the ASMM z-scores. BP percentiles did not differ between the two groups.

A total of 54 BIA assessments (2.5 ± 1.9, range 2–5 per patient) were available for 21 patients with craniopharyngioma during their follow-up. Of the 21 patients with BIA assessments, 18 (85.7%) patients with central hypothyroidism were treated with L-thyroxine at a mean dose of 1.58 ± 0.62 μg/kg/day, to maintain free T4 levels in the upper half of the normal range; 11 (52.3%) patients with GHD received recombinant GH therapy at a mean dose of 20.0 ± 8.13 μg/kg/day, with IGF-1 levels targeted within the normal range for sex, age, and pubertal stage; and 11 (52.3%) patients with adrenal insufficiency were treated with hydrocortisone at a mean dose of 8.57 ± 1.92 mg/m^2/day with dose adjustments according to change in calculated body surface area. In addition, nine (42.8%) patients with arginine-vasopressin deficiency were treated with desmopressin acetate at a dose of 0.32 ± 0.30 μg/day. Three of the four patients who reached puberty-appropriate age and were diagnosed with sex hormone deficiency were boys who received testosterone (50–75 mg/month by intramuscular injections), and one girl was treated with an estradiol patch (12.5 μg). Isolated and combined hormonal deficiencies with appropriate hormonal replacement therapy were documented for 44 (81.5%) BIA assessments as follows: central hypothyroidism in 42 (77.7%), GHD in 24 (44.4%), adrenal insufficiency in 24 (44.4%), arginine-vasopressin deficiency in 21 (38.8%), and sex hormone deficiency at puberty-appropriate age in 11 (Figure 2). Correlation analyses revealed a significant negative association between the individuals' IGF1 z-scores and their FATP ($r_s = -0.445$, $p = 0.007$), without significant associations between IGF1 z-scores and other anthropometric parameters or other body composition components (Table 2).

Table 1. Clinical characteristics, anthropometric parameters, body composition components, and BP percentiles of patients with craniopharyngioma at their last bioimpedance analysis assessment compared to controls.

Variable	Craniopharyngioma	Control	*p* Value
Patients, *n*	21	63	
Males, *n* (%)	13 (63)	39 (63)	
Age (years)	11.6 ± 3.9	11.5 ± 3.3	0.625
Anthropometric measurements			
Height, *z*-score	−0.88 ± 1.00	−0.37 ± 0.78	0.018
Mid-parental height, *z*-score	−0.23 ± 0.95	−0.04 ± 0.76	0.534
Delta height, *z*-score	−0.65 ± 1.27	−0.54 ± 0.77	0.315
Weight, *z*-score	1.10 (−0.33, 1.84)	−0.60 (−1.20, 0.37)	**0.020**
Body mass index, *z*-score	1.71 (0.74, 2.05)	−0.23 (−1.07, 0.50)	**<0.001**
Overweight/obesity	3 (14.3)/11 (52.4)	8 (12.7)/3(5)	**0.017**
Body composition parameters			
Total body FATP	34.2 (23.2, 40.2)	21.5 (18.1, 25.0)	**<0.001**
Truncal FATP	29.5 (23.5, 39.8)	16.5 (13.3, 21.3)	**<0.001**
Trunk-to-total body FATP ratio	0.85 (0.80, 0.90)	0.78 (0.72, 0.82)	**0.012**
Appendicular skeletal muscle mass, *z*-score	−0.06 (−0.99, 0.69)	−0.69 (−1.16, 0.24)	0.313
Muscle-to-fat ratio, *z*-score	−1.78 ± 0.60	−0.52 ± 0.81	**<0.001**
BP			
Systolic percentile	64 (44, 79)	75 (50.8, 89.3)	0.343
Diastolic percentile	65 (55, 86.5)	62.5 (46.5, 80)	0.844

Data are expressed as number and (percent), median (interquartile range), or mean ± standard deviation. Mid-parental height was calculated ((paternal height in cm + maternal height in cm ± 13 cm)/2) and *z*-scores were derived. Delta height, *z*-score presents the difference between the patient's current height *z*-score and the mid-parental height *z*-score. Chi-squared tests were performed to compare categorical variables between groups, and the Mann–Whitney test was performed to compare linear variables with skewed distribution. A *p* value ⩽0.05 was considered significant. Bold indicates significant.
BP, blood pressure; FATP, fat percentage.

Repeated measures linear mixed models analysis indicated that although no notable changes were observed in the BMI and MFR *z*-scores, there was a significant increase over time in the ASMM *z*-score ($B = 0.14$, SE = 0.04, $p = 0.002$), accompanied by a concurrent decline in sex- and age-adjusted FATP ($B = -0.99$, SE = 0.41, $p = 0.018$). MetS components were identified at 21 (38.9%) BIA assessments of 14 (66.7%) patients. The BMI *z*-score of patients at diagnosis of MetS components was higher than that of those without (1.59 ± 1.11 vs 0.68 ± 1.31, $p = 0.05$). Logistic regression models adjusted for sex, age, socioeconomic position, and disease duration revealed that the diagnosis of MetS components was positively associated with FATP (odd ratio = 1.13, CI (1.04, 1.23), $p = 0.006$). MFR and ASMM *z*-scores were not associated with MetS components. The logistic regression models that evaluated the associations between the diagnosis of

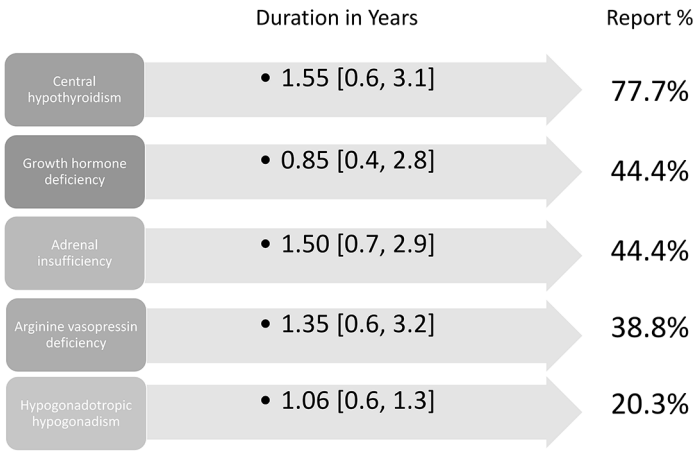


Figure 2. The prevalence of hormonal deficiencies and their median duration at bioimpedance analysis in pediatric patients with craniopharyngioma.

Table 2. Correlation analyses between IGF-1 *z*-scores and various anthropometric and body composition parameters.

Variable	*r*	*p* Value
Height *z*-scores	0.069	0.648
Weight *z*-scores	−0.161	0.284
BMI *z*-scores	−0.258	0.084
FATP	−0.445	**0.007**
ASMM *z*-scores	0.057	0.739
MFR *z*-scores	0.267	0.116

Spearman correlation analyses between IGF-1 *z*-scores and variables. A *p* value of ⩽0.05 was considered significant. Bold indicates significance.
ASMM, appendicular skeletal muscle mass; BMI, body mass index; FATP, fat percentage; MFR, muscle-to-fat ratio.

MetS and body composition components are presented in Table 3.

Discussion

In this observational study, despite contending with obesity, children and adolescents with craniopharyngioma exhibit improvement in body composition over time when provided with timely, appropriate endocrine management. The presence of an unfavorable body composition characterized by higher adiposity indices and a lower MFR did not preclude the possibility of achieving a reduction in adiposity while simultaneously increasing muscle mass. This promising finding suggests that adverse outcomes are not inevitable among survivors of craniopharyngioma. The recognition of the relationship between sex- and age-adjusted FATP to the development of MetS components makes it imperative to develop preventive strategies aimed at limiting the rise in FATP as well as tailor treatments to reduce it.

Craniopharyngioma is treated by surgical removal of the mass followed by radiotherapy when indicated. The surgical approach aims to find a balance between effectively managing the tumor and providing optimal quality of life.[28] While our center promoted a neurosurgical approach that was less invasive, the vast majority of patients nevertheless exhibited postoperative hormonal deficits, many of which had been present prior to

Table 3. Logistic regression models evaluating the association between body composition parameters and the diagnosis of metabolic syndrome components.

Variable	Odds ratio	95% Confidence interval		*p* Value
		Lower	Upper	
Model for FATP				**0.036**
FATP	1.13	1.04	1.23	**0.006**
Sex	2.201	0.60	8.07	0.234
Age	0.859	0.70	1.06	0.156
SEP index	1.434	0.63	3.27	0.391
Disease duration	0.957	0.71	1.28	0.768
Model for ASMM *z*-scores				0.129
ASMM *z*-scores	2.170	1.08	4.34	0.029
Sex	3.050	0.81	11.43	0.098
Age	0.969	0.81	1.15	0.726
SEP index	1.225	0.56	2.68	0.611
Disease duration	0.793	0.61	1.03	0.086
Model for MFR *z*-scores				0.629
MFR *z*-scores	0.846	0.11	6.69	0.874
Sex	4.067	0.28	59.88	0.307
Age	0.822	0.59	1.15	0.248
SEP index	1.147	0.35	3.72	0.819
Disease duration	0.792	0.38	1.65	0.536

Logistic regression models evaluating the association between body composition parameters and the diagnosis of metabolic syndrome components adjusting for sex, age, socioeconomic position, and disease duration. A p value of $\leqslant 0.05$ was considered significant. Bold indicates significance.
ASMM, appendicular skeletal muscle mass; FATP, fat percentage; MFR, muscle-to-fat ratio. SEP, socioeconomic position. The SEP index is an adjusted calculation of 14 variables that measure social and economic levels in four domains: demographics, education, standard of living, and employment.

the surgery. Providing replacement hormonal treatment for children with craniopharyngioma and presenting with hormonal deficiencies is therefore essential for preserving optimal body composition of fat and muscle. GH, thyroid hormones, and sex hormones have anabolic properties, and their combined action results in synergistic effects, stimulating muscle growth and bone accrual.[29,30] Our medical team recommends and oversees the appropriate supplementation of deficient hormones through regular laboratory evaluations. This practice may play a role in the satisfactory muscle mass levels observed in our patients with craniopharyngioma, which was found to be comparable to that of the control group.

The regulation of adiposity by hormones encompasses both direct and indirect effects. GH stimulates lipolysis through intracellular activation of the MEK–ERK pathway, which results in phosphorylation of peroxisome proliferator-activated receptor-γ, thereby increasing insulin sensitivity.[31] Thyroid hormones stimulate the

basal metabolic rate by increasing adenosine triphosphate production and maintaining ion gradients. They also directly impact adipose tissue, as demonstrated by the browning of white adipose cells, leading to a sustained increase in thermogenic activity over time.[32]

Our patients with craniopharyngioma demonstrated elevated BMI *z*-scores and a higher incidence of obesity, together with body composition marked by increased adiposity, despite close endocrine monitoring with hormonal supplementation in accordance with guidelines. This combination may result from the often-reported delay in diagnosis seen in patients with craniopharyngioma attributable to the tumor's slow growth.[28] Olsson et al.[33] observed that the initiation of recombinant GH therapy following tumor resection may also be postponed due to concerns about tumor recurrence, despite the low reported risk of recurrence. Despite our observation of gradual improvements in weight status and body composition components, the delay in diagnosis and subsequent postponement of hormonal replacement therapies may leave a gap in time that cannot be entirely resolved.

Twenty-four of our reported patients did not receive supplementation with sex hormones, either because of their young age or because there was evidence of intact functioning of the hypothalamic-pituitary-gonadal axis. The nine adolescents (six boys and three girls) who received sex hormone supplementation included four boys who were categorized with obesity. Noteworthy, a rapid weight gain due to accelerated accumulation of fat in boys may be associated with lower testosterone levels,[34] in which case a higher dose supplementation may be required. The rarity of craniopharyngioma precluded our ability to arrive at any significant conclusions, and the limited availability of published guidelines necessitated our tailoring of individualized treatments for each case.

Obesity exacts a metabolic toll, potentially leading to the early onset of the development of cardiovascular complications in young individuals. Of note, two-thirds of the children with craniopharyngioma in our study exhibited obesity and MetS components, consistent with previous research.[17,18] Our analysis revealed that FATP adjusted for sex and age predicted the diagnosis of MetS components, whereas such an interaction was not observed with muscle indices. This observation underscores the importance of the early prevention of adiposity accumulation in patients when diagnosed as having craniopharyngioma.

Hypothalamic obesity is a well-recognized complication of craniopharyngioma and is frequently observed in patients with childhood-onset craniopharyngioma.[18,35] Given that the risk of hypothalamic obesity reportedly escalates with the extent of the neurosurgical resection. There is a growing trend toward advocating for more conservative surgical approaches.[36] Diagnosis predominantly relies upon clinical evaluation, emphasizing the identification of hyperphagia, accelerated weight gain, and laboratory evidence indicating insulin imbalance.[37] This condition involves vagally mediated hyperinsulinemia contributing to enhanced lipogenesis.[36] Decreased hypothalamic responsiveness to leptin and ghrelin results in elevated energy intake. This is coupled with compromised energy expenditure due to a reduced sympathetic tone, which further deteriorates the problem.[38]

Managing hypothalamic obesity poses significant challenges, often requiring strict dietary modifications, promoting physical activity, and considering pharmacological interventions.[36] Incretin-based glucagon-like peptide 1 receptor agonist therapies present promising new treatment avenues,[36] although none of this study's participants had initiated treatment during the study period. Bariatric surgery may emerge as a potential strategy to address obesity in cases where pharmacological responsiveness is limited.[39] Further studies on the effectiveness of these therapeutic modalities are warranted.

This observational study has several limitations that bear mention. It is retrospective in design and was conducted at a single tertiary center. The rarity of the diagnosis inevitably led to a small sample size that may limit the generalizability of findings. Nevertheless, the longitudinal design facilitates the examination of changes over time in a real-life setting, offering insights into disease progression and treatment outcomes within a specialized neurosurgical center. Moreover, the comparison of the patients with a sex and age-matched control group provides context for understanding the unique characteristics and challenges faced by children with craniopharyngioma.

Conclusion

The results of this study revealed that individuals who survived craniopharyngioma surgery exhibited adverse alterations in body composition in the form of increased adiposity. They were followed up and treated in the pediatric endocrine clinic, during which time they demonstrated an improvement in body composition. The link between sex- and age-adjusted FATP and components of MetS underscores the importance of preventive strategies aimed at limiting FATP increase and customizing treatments, including hormone replacement therapies, to effectively control adiposity accumulation, manage metabolic decline, and enhance muscle growth in this vulnerable population. Further research is needed to evaluate the long-term efficacy of these interventions and optimize outcomes for pediatric craniopharyngioma patients.

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Tel Aviv Sourasky Medical Center review board, approval number (065-18-TLV). Due to the retrospective nature of the study, the review board waived the requirement for informed parental consent.

Consent for publication

Not applicable.

Author contributions

Hussein Zaitoon: Conceptualization; Data curation; Investigation; Methodology; Project administration; Software; Visualization; Writing – original draft.

Ori Eyal: Conceptualization; Data curation; Writing – review & editing.

Michal Yackobovitch-Gavan: Formal analysis; Software; Writing – review & editing.

Ravit Regev: Conceptualization; Data curation; Writing – review & editing.

Yael Issan: Conceptualization; Data curation; Writing – review & editing.

Jonathan Roth: Conceptualization; Data curation; Writing – review & editing.

Shlomi Constantini: Conceptualization; Data curation; Writing – review & editing.

Yael Lebenthal: Conceptualization; Data curation; Writing – review & editing.

Avivit Brener: Conceptualization; Investigation; Methodology; Project administration; Software; Supervision; Validation; Writing – original draft.

Acknowledgements

The authors thank Esther Eshkol for editorial assistance. A portion of this research has been presented at ESPE 2024, taking place from November 16 to 18, 2024, in Liverpool, England.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated during and/or analyzed for the current study are available from the corresponding author upon reasonable request.

ORCID iDs

Hussein Zaitoon https://orcid.org/0000-0002-4979-3799

Avivit Brener https://orcid.org/0000-0002-2742-8264

Supplemental material

Supplemental material for this article is available online.

References

1. Zacharia BE, Bruce SS, Goldstein H, et al. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. *Neuro Oncol* 2012; 14: 1070–1078.
2. Van Schaik J, Hoving EW, Müller HL, et al. Hypothalamic-pituitary outcome after treatment for childhood craniopharyngioma. *Front Horm Res* 2021; 54: 47–57.
3. Gabay S, Merchant TE, Boop FA, et al. Shifting strategies in the treatment of pediatric

craniopharyngioma. *Curr Oncol Rep* 2023; 25: 1497–1513.

4. Mortini P, Losa M, Pozzobon G, et al. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. *J Neurosurg* 2011; 114: 1350–1359.
5. Bogusz A and Müller HL. Childhood-onset craniopharyngioma: latest insights into pathology, diagnostics, treatment, and follow-up. *Expert Rev Neurother* 2018; 18: 793–806.
6. Gupta DK, Ojha BK, Sarkar C, et al. Recurrence in pediatric craniopharyngiomas: analysis of clinical and histological features. *Childs Nerv Syst* 2006; 22: 50–55.
7. Li Q, You C, Liu L, et al. Craniopharyngioma cell growth is promoted by growth hormone (GH) and is inhibited by tamoxifen: involvement of growth hormone receptor (GHR) and IGF-1 receptor (IGF-1R). *J Clin Neurosci* 2013; 20: 153–157.
8. Nyberg F and Hallberg M. Growth hormone and cognitive function. *Nat Rev Endocrinol* 2013; 9: 357–365.
9. Moøller N and Joørgensen JOL. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev* 2009; 30: 152–177.
10. Dixit M, Poudel SB and Yakar S. Effects of GH/IGF axis on bone and cartilage. *Mol Cell Endocrinol* 2021; 519: 111052.
11. Heinks K, Boekhoff S, Hoffmann A, et al. Quality of life and growth after childhood craniopharyngioma: results of the multinational trial KRANIOPHARYNGEOM 2007. *Endocrine* 2018; 59: 364–372.
12. Sirigiri S, Vaikkakara S, Sachan A, et al. Correction of hypothyroidism leads to change in lean body mass without altering insulin resistance. *Eur Thyroid J* 2016; 5: 247.
13. Laitinen EM, Hero M, Vaaralahti K, et al. Bone mineral density, body composition and bone turnover in patients with congenital hypogonadotropic hypogonadism. *Int J Androl* 2012; 35: 534–540.
14. Sterkenburg AS, Hoffmann A, Gebhardt U, et al. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro Oncol* 2015; 17: 1029–1038.
15. Rovani S, Butler V, Samara-Boustani D, et al. Long-term weight gain in children with craniopharyngioma. *Eur J Endocrinol* 2024; 190: 363–373.
16. Joly-Amado A, Cansell C, Denis RGP, et al. The hypothalamic arcuate nucleus and the control of peripheral substrates. *Best Pract Res Clin Endocrinol Metab* 2014; 28: 725–737.
17. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, et al. The metabolic syndrome and its components in 178 patients treated for craniopharyngioma after 16 years of follow-up. *Eur J Endocrinol* 2018; 178: 11–22.
18. Jazbinšek S, Kolenc D, Bošnjak R, et al. Prevalence of endocrine and metabolic comorbidities in a national cohort of patients with craniopharyngioma. *Horm Res Paediatr* 2020; 93: 46–57.
19. Czeczelewski M, Czeczelewski J, Czeczelewska E, et al. Association of body composition indexes with cardio-metabolic risk factors. *Obes Med* 2020; 17: 100171.
20. Brener A, Peleg I, Rosenfeld T, et al. Beyond body mass index—body composition assessment by bioimpedance in routine endocrine practice. *Endocr Pract* 2021; 27: 419–425.
21. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Heal Stat* 11 2002; (246): 1–190.
22. Barlow SE and Dietz WH. Obesity evaluation and treatment: expert committee recommendations. *Pediatrics* 1998; 102: E29.
23. Cole TJ, Flegal KM, Nicholls D, et al. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 2007; 335: 194.
24. Shypailo RJ. Age-based pediatric blood pressure reference charts. Baylor College of Medicine, Children's Nutrition Research Q21 Center, Body Composition Laboratory, http://www.bcm.edu/bodycomplab/BPappZjs/BPvAgeAPPz.html (2018, accessed 10 March 2024).
25. Orsso CE, Gonzalez MC, Maisch MJ, et al. Using bioelectrical impedance analysis in children and adolescents: pressing issues. *Eur J Clin Nutr* 2022; 76(5): 659–665.
26. McCarthy HD, Samani-Radia D, Jebb SA, et al. Skeletal muscle mass reference curves for children and adolescents. *Pediatr Obes* 2014; 9: 249–259.

27. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017; 140: e20171904.

28. Cohen M, Guger S and Hamilton J. Long term sequelae of pediatric craniopharyngioma—literature review and 20 years of experience. *Front Endocrinol (Lausanne)* 2011; 2: 81.

29. Gharahdaghi N, Phillips BE, Szewczyk NJ, et al. Links between testosterone, oestrogen, and the growth hormone/insulin-like growth factor axis and resistance exercise muscle adaptations. *Front Physiol* 2021; 11: 621226.

30. Geffner M, Lundberg M, Koltowska-Häggström M, et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). *J Clin Endocrinol Metab* 2004; 89: 5435–5440.

31. Kopchick JJ, Berryman DE, Puri V, et al. The effects of growth hormone on adipose tissue: old observations, new mechanisms. *Nat Rev Endocrinol* 2020; 16: 135–146.

32. Volke L and Krause K. Effect of thyroid hormones on adipose tissue flexibility. *Eur Thyroid J* 2021; 10: 1–9.

33. Olsson DS, Buchfelder M, Wiendieck K, et al. Tumour recurrence and enlargement in patients with craniopharyngioma with and without GH replacement therapy during more than 10 years of follow-up. *Eur J Endocrinol* 2012; 166(6): 1061–1068.

34. Kim C, Harrall KK, Glueck DH, et al. Childhood adiposity and adolescent sex steroids in the exploring perinatal outcomes among children study. *Clin Endocrinol (Oxf)* 2019; 91: 525–533.

35. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, et al. Excess morbidity and mortality in patients with craniopharyngioma: a hospital-based retrospective cohort study. *Eur J Endocrinol* 2018; 178: 93–102.

36. Gan H-W, Cerbone M and Dattani MT. Appetite- and weight-regulating neuroendocrine circuitry in hypothalamic obesity. *Endocr Rev* 2024; 45(3): 309–342.

37. Rachmasari KN, Strauss SB, Phillips CD, et al. Posterior hypothalamic involvement on pre-operative MRI predicts hypothalamic obesity in craniopharyngiomas. *Pituitary* 2023; 26: 105–114.

38. Roth C, Wilken B, Hanefeld F, et al. Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. *Eur J Endocrinol* 1998; 138: 89–91.

39. Van Santen SS, Wolf P, Kremenevski N, et al. Bariatric surgery for hypothalamic obesity in craniopharyngioma patients: a retrospective, matched case-control study. *J Clin Endocrinol Metab* 2021; 106: e4734–e4745.