Exploring eating behavior and psychological mechanisms associated with obesity in patients with craniopharyngioma: a scoping review protocol

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ABSTRACT

Objective: The objective of the review is to explore the evidence on the behavioral and psychological mechanisms underlying the development of obesity in patients with craniopharyngioma. The review will map the available evidence, identify gaps in the literature, and find avenues of future intervention.

Introduction: Craniopharyngiomas are low-grade intracranial tumors of the supersellar region. Obesity is associated with the tumor or surgery or radiotherapy to treat the tumor; however, the behavioral and psychological processes contributing to that association are not clear. This review will provide a synthesized evidence base of the relevant research.

Inclusion criteria: This review will consider published studies with all types of study designs, including patients with childhood- or adult-onset craniopharyngioma. Articles assessing factors that may impact eating behavior will be included based on the following categories: eating behavior, obesity, neuroimaging, endocrine response, energy expenditure, sleep, and neuropsychology.

Methods: MEDLINE, Embase, and PsycINFO will be searched, in addition to the Cochrane Library, Web of Science, Scopus, ClinicalTrials.gov, NICE evidence search, and International Standard Randomised Controlled Trial Number (ISRCTN). No limits will be placed on the scope of the search. The methodology will follow a three-stage process with two independent reviewers at each stage, including an initial database search, screening of titles and abstracts of retrieved studies, full-text assessment for inclusion criteria, and hand-searching of reference lists. Data will be extracted using a standardized charting form and summarized in tables. The data will be synthesized using a narrative summary and diagrammatic map and will be based on the evidence for each of the proposed research categories.

Keywords: energy expenditure; entero-endocrine; fMRI; hyperphagia; hypothalamus

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Introduction

Craniopharyngiomas are low-grade intracranial tumors originating from ectoblastic remnants of the Rathke pouch.[1] They can arise anywhere along the craniopharyngeal canal, but mostly occur in the sellar and parasellar regions, resulting in anatomical proximity to the optic chiasm and the hypothalamic-pituitary axis.[2] There are two distinct histological subtypes: adamantinomatous and papillary.[3] The incidence of craniopharyngiomas is rare, with 0.5 to two cases per million people per year.[4] There is a bimodal age distribution: the first peak in detection occurs in children and adolescents aged five to 14 years (childhood onset), consisting virtually exclusively of the adamantinomatous subtype, and the second peak occurs in adults aged 50 to 74 years (adult onset), which consists of both subtypes.[5]

Treatment options include neurosurgical resection, radiation therapy, and intracystic treatments; such

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options have been recently assessed through systematic reviews.[eg,6,7] There has been a shift in management strategies toward less invasive surgery with the addition of radiotherapy (previously photon but more recently with proton radiotherapy). The overall survival rate at five years is 83% to 96% in children and 54% to 96% in adults.[2] Craniopharyngiomas are associated with substantially reduced quality of life due to tumor and treatment-related sequelae.[8] These commonly include significant endocrine dysfunction,[9] visual field deficits, obesity,[2] and excess morbidity and mortality.[10] While obesity in craniopharyngioma is undoubtedly multifactorial in origin, hypothalamic damage is often a comorbidity.[2]

Hypothalamic obesity describes obesity secondary to dysfunction or damage to the hypothalamic satiety-regulating pathways and hypothalamic connections to other brain regions involved in food intake and can lead to major perturbations in energy balance.[11] Individuals with hypothalamic obesity have excessive, rapid, and intractable weight gain potentially associated with hyperphagia and abnormal food-seeking behaviors, and it is often unresponsive to diet or exercise.[11] However, the role of these mechanisms in the development of obesity in craniopharyngioma is complex and poorly (or insufficiently) studied.[12] Obesity has a high prevalence rate, occurring in approximately 50% of craniopharyngioma patients.[13] It increases the risk of metabolic and cardiovascular disease[7] and has a profound negative impact on quality of life.[14] Yet despite this significant morbidity, there are no effective weight-loss interventions.[6,7]

Several factors have been identified that may contribute to weight gain and subsequent obesity in patients with craniopharyngioma over and above known hypothalamic-pituitary-adrenal axis (HPA) dysfunction.[12] These include hyperphagic eating behavior,[15] lower energy expenditure,[16] reduced physical activity,[17] dysfunction of entero-endocrine responses,[18] and altered brain responses to food cues.[19] Reduced physical activity levels have been identified, rather than increased energy intake,[17] which may be due to other symptoms, such as increased insomnia and daytime sleepiness, potentially leading to increased insulin resistance in these patients.[12] Hoffman *et al.*[15] reported greater pathological and disordered eating in severely obese patients with craniopharyngioma but noted that this disordered eating was not specific to those with craniopharyngioma. Preliminary evidence from our group has suggested that hyperphagic eating scores are positively correlated with both standardized body mass index (BMI SDS) and energy intake in a single meal.[20] Overall, there is a lack of research specifically investigating eating behavior in patients with craniopharyngioma. Prior to conducting further research on how eating behavior may be affected by craniopharyngioma, a scoping review of the available literature is required.

Damage to the hypothalamus from the tumor or treatment affects peripherally secreted hormones; elevated leptin and insulin have been reported in craniopharyngioma compared with patients with common obesity.[21] Non-elevated or reduced fasting ghrelin secretion and post-prandial ghrelin suppression has been found in obese patients with adult-onset craniopharyngioma,[22] which may further lead to changes in appetite and disordered eating in these patients. Moreover, patients with anterior hypothalamic damage through craniopharyngioma present with a significantly lower fasting level of oxytocin (involved in metabolism and behavior) compared with craniopharyngioma patients with no damage or anterior and posterior damage.[23]

It is possible that the hypothalamic damage following craniopharyngioma may have widespread effects on the brain. Research has begun to assess these potential effects using functional magnetic resonance imaging (MRI)[24]; for example, a pilot study of four patients with craniopharyngioma and four controls demonstrated a trend toward higher activation of the nucleus accumbens, insula, and medial orbitofrontal cortex following a test meal in patients, suggesting that perception of food cues may be altered in this population.[19] This result has recently been corroborated by a study from our group, showing differential neural responses to food cues in nine young people with craniopharyngioma compared with BMI SDS and gender-matched controls (Elsworth *et al.*, personal communication). Another functional MRI study has shown impaired memory retrieval in the prefrontal cortex in patients with craniopharyngioma[25]; this corroborates a further study demonstrating neuropsychological deficits in patients with craniopharyngioma.[26]

To develop novel weight-loss interventions, we may need to take a step back to gain a different perspective to improve our understanding of the

etiology of obesity associated with craniopharyngioma. This scoping review will explore the existing literature on the psychological aspects of eating behavior, and how other potential factors affecting energy balance may influence eating behavior in craniopharyngioma. It is important to note that this proposed review will not substantially overlap with the recent systematic review by van Iersel *et al.*,[7] as that review had a much broader scope, including interventions in four modalities across six clinical domains. While van Iersel and colleagues did include hyperphagia as one clinical domain, the focus of their search was on dietary intake rather than psychological aspects of eating behavior (eg, disinhibited eating) or mechanisms underlying behavior towards food (eg, neural basis to food cues).

Preliminary searches with strict inclusion criteria have been conducted on the following databases: MEDLINE (74 potential papers for inclusion), Embase (218 potential papers for inclusion), and PsycINFO (seven potential papers for inclusion). Moreover, while there are excellent recent reviews providing an overall picture of clinical outcomes and interventions in craniopharyngioma,[(eg,7)] our searches revealed no formal scoping reviews exploring the psychological aspects of eating behavior and how factors affecting energy balance may influence eating behavior in craniopharyngioma.

Review questions

i. What research has been conducted to date that addresses eating behavior in patients with craniopharyngioma?

This question will allow us to map what is currently known about the pathophysiology of eating behavior in this patient group, according to the concepts outlined below. Following this primary question, we plan to separately synthesize and map the research on patients with craniopharyngioma: ii) with and without obesity and iii) with childhood or adult onset of the tumor.

Finally, we will explore iv) whether the research conducted to date has simply measured eating behavior in this patient group or whether interventions to improve eating behavior (and appropriate comparators) have been assessed. We will map these findings and summarize any recommendations for future research and intervention design. The findings from this last question may identify gaps in the literature, a key aim of a scoping review, which can be addressed through future research, with a view to designing interventions to improve eating behavior and/or quality of life in patients with craniopharyngioma.

Inclusion criteria

Participants

This review will consider evidence from pediatric and adult populations with childhood-onset and adult-onset craniopharyngioma, including studies in which the patients were diagnosed and/or tested as children or adults. Only those with craniopharyngioma will be included; other forms of hypothalamic obesity will be excluded. The evidence suggests that those with craniopharyngioma (compared with other tumors) may have greater hormonal imbalance[(eg,27)] or a greater risk of weight gain[(eg,28)]; however, studies involving patients with craniopharyngioma often contain mixed populations due the rarity of the tumor. Therefore, we will only include studies with mixed populations if the craniopharyngioma group comprises >50% of the sample and is clearly identified, and if the results from this group are reported separately. Patients with craniopharyngioma of all weight status at the time the research was conducted will be included, and there will be no restriction on age or sex. Research with animals will not be included.

Concept

This review will have a narrow focus, primarily on eating behavior, but also on other factors that may influence eating behavior in patients with craniopharyngioma. By employing this narrow criteria, we will ensure the novel contribution of this scoping review, in light of the broader systematic review of interventions recently published.[7] Primarily, the focus of the review will be on the following behavioral and psychological mechanisms:

- Eating behavior: the research in this section pertains to evaluating the behavioral and psychological underpinnings of eating behavior in patients with craniopharyngioma. Eating behavior may include research on hyperphagia, nutrition, appetite, hunger, satiety, ad libitum eating, portion size, disinhibited eating, dietary restraint, emotional eating, external eating, food reinforcement, food reward, food addiction, binge eating, and satiety responsiveness.

Secondly, papers assessing the following phenomena of interest in light of their impact on eating behavior will be included:

- Obesity: This refers to obesity, overweight, BMI (kg/m^2), fat, adiposity using auxology, bioimpedance, MRI, or dual energy X-ray absorptiometry measures.
- Imaging studies: There are several small neuroimaging studies that have been conducted to study the impact of craniopharyngioma on brain functioning, specifically relating to the neural response to food cues and a memory task. The keywords for this area will be functional magnetic resonance imaging (fMRI) and MRI.
- Endocrine responses: From a clinical perspective, patients with craniopharyngioma are primarily seen in endocrine clinics. As such, there has been a greater focus on research on HPA hormonal changes associated with craniopharyngioma. For the purposes of this review, controlling for adequate HPA endocrine assessment and replacement will be important to avoid confounding factors of the other phenomena of interest central to this review. However, research on enteroendocrine factors, such as glucagon-like peptide1 (GLP1), neuropeptide Y (NPY), gastrin, ghrelin, and peptide YY (PYY) will be included, as well as other relevant hormones (oxytocin, leptin, insulin, prolactin, endocannabinoids) due to their impact on eating behavior.
- Energy expenditure: Several studies have reported a reduction in energy expenditure in patients with craniopharyngioma. This could have an impact on the eating behavior seen in this patient group; therefore, the following terms will be included in the search strategy: resting metabolic rate, basal metabolic rate, energy expenditure.
- Sleep studies: Several recent studies have suggested that sleep may be negatively affected by craniopharyngioma and/or treatment. Studies considering the impact of sleep disturbance on eating behavior will be included.
- Neuropsychology: There are a few studies presenting evidence that neuropsychological function may be impaired in craniopharyngioma, which may influence eating behavior.

Context

The existing research on the phenomena of interest is diverse and has been conducted in numerous settings. Primarily, research on patients with craniopharyngioma has been conducted in a hospital setting with health care professionals, but this is not exclusively the case. No restrictions will be placed on the studies included in this review based on the setting in which the research took place.

Types of studies

Considering the very specific scope of this review on eating behavior and psychological mechanisms underlying obesity in craniopharyngioma, and the limited evidence base in the literature, all types of primary research will be considered. This will include, quantitative, qualitative and mixed method study designs, such as peer-reviewed publications, accepted conference abstracts, and expert opinion consensus guidelines, if identified. This will ensure the scoping review captures all research that has incorporated relevant measures. Evidence in this review will not be restricted by country, language, or date to allow the full scope of the existing research to be included.

Methods

This review has been developed following both the JBI methodology[29] and the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR).[30]

Search strategy

Following the guidance from JBI, a three-phase search will be conducted to find eligible papers according to the inclusion criteria. An initial search of MEDLINE, Embase, and PsycINFO via Ovid was conducted. This was followed by an analysis of title and abstract text words plus index terms used to describe articles. This initial search informed the design of the full search, which was adapted for each of the databases to be searched, with assistance from a professional librarian. The search strategy to be employed in MEDLINE is shown in Appendix I. The following databases will be searched: MEDLINE (Ovid), Excerpta Medica Database (Embase), PsycINFO (Ovid), Web of Science, and Scopus. The following trial registers will also be searched: ISRCTN (International Standard Randomised Controlled Trial Number), ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, and National Institute for Health and Care Excellence (NICE). The third phase of the strategy will involve searching

the reference list of all included articles for additional relevant studies.

Study selection

All citations identified through the search will be downloaded and organized into EndNote v.X9 (Clarivate Analytics, PA, USA). Any duplicates will be removed. Titles and abstracts will be screened by two independent reviewers for assessment against the inclusion criteria; full texts of those papers that meet the inclusion criteria will be retrieved. The full texts will then be assessed in more detail by two independent reviewers. Articles that do not meet the inclusion criteria will be excluded, with full details of the reasoning for that decision provided in an appendix in the final review paper. A third reviewer will be brought into the discussions if it is not clear whether an article should be included. The final scoping review will report the review decision process, identifying the number of papers located, removed due to duplication or exclusion, and included as full texts at each step of the process and presented in a PRISMA flow diagram.[30]

Data extraction

The data from each of the included articles will be extracted using the draft charting form shown in Appendix II. Charting of the results will be completed for each article by two independent reviewers, following a test extraction of at least two articles. Any disagreements that arise between the reviewers will be resolved through discussion with a third reviewer. Data will be extracted based on the following fields[31]: author(s); year of publication; country of origin; objectives; age of study population at time of study; age at diagnosis (childhood or adult-onset craniopharyngioma); sample size; methodology; details of any intervention or experimental conditions and comparator(s); concept; measurement of outcomes; and key findings that relate to obesity and eating behavior in craniopharyngioma. During the review, the charting form may be updated to allow full extraction of the relevant data; the final version will be included in the final review article. If further clarification is required, authors of included articles may be contacted.

Data presentation

To address the primary research question, the review results will be presented in tabular format and will be organized according to onset category and outcome variables measured, and within those categories, according to study design or article type. This will be done to incorporate an overview of the levels of evidence provided by the different studies (causality, associations, or expert opinions on clinical practice). A draft results table is shown in Appendix III. This may be adapted during the review process to ensure the most relevant results are presented with clarity. A diagrammatic map will also be developed to present the research categories described in the concept section, and a narrative summary will synthesize this data.

To address the second and third questions posed by this review, two additional diagrammatic maps will be produced to synthesize the research pertaining to patients with craniopharyngioma[2] with and without obesity[3] and childhood or adult onset of the tumor.

Finally, to address the fourth question, which aims to map existing literature that has tested interventions to improve eating behavior in patients with craniopharyngioma, a table of intervention studies will be drawn up and results synthesized based on study design, patient group, and the relevant aspect of eating behavior measured.

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Appendix I: Search Strategy

MEDLINE (Ovid)
Date searched: April 16, 2021

#	Searches	Records Retrieved
1	Craniopharyngioma/	4569
2	craniopharyngioma.tw.	3305
3	1 or 2	5495
4	Hyperphagia/	3222
5	hyperphagia.tw.	3830
6	Nutrition Surveys/ or Parenteral Nutrition, Total/ or Nutrition Assessment/ or Nutrition Therapy/ or Parenteral Nutrition, Home/ or Infant Nutrition Disorders/ or Parenteral Nutrition/ or Nutrition Disorders/ or Enteral Nutrition/ or Child Nutrition Disorders/ or Parenteral Nutrition Solutions/ or Nutrition Policy/	106,090
7	nutrition.tw.	160,248
8	Appetite Depressants/ or Appetite/ or Appetite Stimulants/ or Appetite Regulation/	15,146
9	appetite.tw.	25,938
10	hungr*.tw.	2323
11	hunger*.tw.	9747
12	Hunger/	5540
13	Satiety Response/ or Satiation/ or Feeding Behavior/	89,472
14	satiat*.tw.	4049
15	satiet*.tw.	9413
16	("ad libitum" adj2 eat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	197
17	("ad libitum" adj2 meal).mp.	353
18	(food adj2 reinforc*).mp.	2507
19	(eating adj2 behavio*).mp.	12,043
20	(feeding adj2 behavio*).mp.	91,505
21	Portion Size/	540
22	(portion adj2 siz*).mp.	2232
23	(disinhibit* adj2 eat*).mp.	301
24	(disinhibit* adj2 feed*).mp.	39
25	(diet* adj2 restriction).mp.	7908
26	(diet* adj2 restraint).mp.	1249
27	(diet* adj2 limit*).mp.	1446

(*Continued*)

#	Searches	Records Retrieved
28	(emotion* adj2 eat*).mp.	1373
29	(emotion* adj2 feed*).mp.	261
30	(external adj2 eat*).mp.	308
31	(external adj2 feed*).mp.	620
32	(food adj2 reward).mp.	2246
33	(food adj2 addict*).mp.	786
34	(eat* adj2 addict*).mp.	265
35	"dutch eating behaviour questionnaire".mp.	107
36	"dutch eating behavior questionnaire".mp.	173
37	"three factor eating questionnaire".mp.	557
38	"child eating behaviour questionnaire".mp.	43
39	"child eating behavior questionnaire".mp.	63
40	"adult eating behaviour questionnaire".mp.	5
41	"adult eating behavior questionnaire".mp.	7
42	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	368,484
43	"magnetic resonance imag*".tw.	240,452
44	neuroimag*.tw.	50,777
45	mri.tw.	250,048
46	fmri.tw.	42,036
47	"functional magnetic resonance imag*".tw.	31,245
48	43 or 44 or 45 or 46 or 47	436,509
49	Ghrelin/	7574
50	ghrelin.tw.	10,221
51	Leptin/	24,094
52	leptin.tw.	35,289
53	Neuropeptide Y/ or Peptide YY/ or Gastrointestinal Hormones/ or Glucagon-Like Peptide 1/	25,156
54	neuropeptide Y.tw.	13,297
55	"Peptide YY".tw.	2557
56	"Glucagon-Like Peptide 1".tw.	11,596
57	Insulin/	187,219
58	insulin.tw.	363,420
59	NPY.tw.	10,584
60	PYY.tw.	2486

(*Continued*)

#	Searches	Records Retrieved
61	GLP1.tw.	505
62	Oxytocin/	20,055
63	oxytocin.tw.	22,961
64	Gastrins/	12,637
65	gastrin.tw.	15,571
66	Prolactin-Releasing Hormone/ or Prolactin/ or Prolactin Release-Inhibiting Factors/ or Receptors, Prolactin/	40,497
67	prolactin.tw.	42,300
68	Endocannabinoids/	5978
69	Endocannabinoid*.tw.	8733
70	Gastrointestinal Hormones/	6190
71	(gastrointestinal adj2 hormon*).tw.	2216
72	(gut adj2 hormon*).tw.	2493
73	(gastrointestinal adj2 peptide*).tw.	852
74	(gut adj2 peptide*).tw.	1409
75	Cholecystokinin/ or Receptors, Cholecystokinin/	12,508
76	cholecystokinin.tw.	14,174
77	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76	565,982
78	Basal Metabolism/	8341
79	basal metabolic rate*.tw.	2679
80	rest* metabolic rate*.tw.	3009
81	Energy Metabolism/	84,219
82	(energy adj2 metabol*).tw.	43,884
83	(energy adj2 expend*).tw.	27,042
84	Calorimetry/ or Calorimetry, Indirect/	16,312
85	calorimet*.tw.	42,991
86	78 or 79 or 80 or 81 or 82 or 83 or 84 or 85	172,135
87	hypothalam*.tw.	119,172
88	(hypothalam* adj2 damag*).mp.	358
89	Pediatric Obesity/ or Obesity/ or Obesity Management/ or Obesity, Morbid/	215,947
90	obes*.tw.	310,837
91	Overweight/	26,351
92	(over adj2 weight).tw.	5383
93	overweight.tw.	71,798

(*Continued*)		
#	**Searches**	**Records Retrieved**
94	"body mass index".tw.	190,779
95	BMI.tw.	150,510
96	(body adj2 weight).tw.	216,792
97	fat.tw.	270,218
98	adipos* .tw.	111,259
99	89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98	917,941
100	Sleep/	55,363
101	sleep.mp.	200,908
102	Neuropsychology/	2454
103	neuropsych* .mp.	157,238
104	100 or 101	200,908
105	102 or 103	157,238
106	42 or 48 or 77 or 86 or 87 or 88 or 99 or 104 or 105	2,510,922
107	3 and 42 and 106	74

Not restricted by language.

Appendix II: Draft data extraction form

Reviewer	
Date	
Record No.	
Author(s)	
Journal/Source	
Year of publication	
Source:	
Publication type	(eg, peer-reviewed article, unpublished thesis)
Evidence type	(eg, research or expert opinion)
Inclusion criteria	
Exclusion criteria	
Population:	
CR group*	
Childhood or adult onset	
Mean age at time of study	
Mean BMI of group	
No. of patients in each BMI category	<18 underweight; 18–24.9 healthy weight; 25–29.9 overweight; 30–39.9 obese; 40 morbidly obese>
Sample size	
Comparator group?	(Insert main characteristic of comparator group)
Matched to CR group?	(If yes, using which characteristics?)
Mean age of group	
Mean BMI of group	
Sample size	
Concept:	
Objectives	

Design (including details of any intervention or experimental conditions)	Options: RCT – crossover RCT – parallel arms Quasi-experimental – single arm Quasi-experimental – non-randomized trial (no control) Quasi-experimental – non-randomized trial (with control) Cross-sectional Cohort study Case-control study Case study/case series Qualitative – interviews Qualitative – focus groups Other (specified: free text) Not applicable
Phenomena of interest	Options: i) eating behavior (EB); ii) EB and imaging; iii) EB and endocrine response; iv) EB and energy expenditure; v) EB and sleep; EB and neuropsychology
Outcomes measures	(eg, levels of hormones, scores on EB questionnaires, neuroimaging measures, qualitative interviews etc.)
Key findings	
Key recommendations	
Context:	
Country	
Setting	Options: Hospital – inpatient Hospital – outpatient Community – clinic Community – care home Community – home Other (specified: *free text*) Not specified
Comments	

BMI, body mass index; CR, craniopharyngioma; EB, eating behavior; RCT, randomized controlled trial.

Appendix III: Draft results table

Reference	Year	Population	Authors	Design	Measured outcomes	Key findings	Key recommendations	Country	Publication type
Citation	Year of publication	Onset category Age at study Level of obesity	Full names	RCT, case-control study, etc. Details of control group	Details of the overall category of study (see concept above) and the outcomes measured in the study	Main results	Any recommendations for future research or interventions	Country where research took place and setting	Peer-review article, unpublished report, consensus guidelines etc.

RCT, randomized controlled trial