Hypothalamic Obesity Effects on Childhood Outcomes, Risks Factors, and Possible Treatments

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Background

- Hypothalamic obesity (HO) is a rarely seen treatment-resistant obesity that occurs commonly in people with brain tumors of the hypothalamus and pituitary gland, such as craniopharyngioma (CP).
- CP is a rare grade 1 tumor that is frequently treated surgically. These tumors, as well as their substantial surgical removal, can both harm the hypothalamic regions that regulate metabolism, resulting in HO.
- Affected patients have lower resting energy expenditure (REE) and frequently have uncontrolled hunger, both of which are significant pathogenic variables.[1,2]
- Individuals with CP who acquire HO have an increased lifetime mortality rate, which is mediated by an increased burden of obesity-related comorbidities such as fatty liver disease, type 2 diabetes mellitus, and cardiovascular disease.[2]
- The goal of this literature review is to establish how HO affects childhood development, HO risk factors, and potential HO treatment options.

Methods

- The Tennessee Technological University Library Database Eagle Search, Frontiers in Endocrinology, Neuro-Oncology, Pediatric Obesity, Endocrine Connections, PLOS One, International Journal of Obesity, and Journal of the Endocrine Society were searched to discover the research articles.
- The search was limited to peer-reviewed articles published in the last 10 years utilizing related keywords such as: hypothalamic obesity, pediatric craniopharyngioma, social function, brain tumor, quality of life, mortality, resting energy expenditure, hypothalamic damage/injury, dextroamphetamine, treatment, and more. The goal was to be as specific as possible while also finding articles that similar discussed the same issues HO and how it is affected by these factors.

Discussion

HO and Childhood Development

- First, a subset of pediatric patients attempted medication for weight loss, even though the majority found lifestyle changes unsatisfactory.[3]
- They discovered that, whereas 83% of caregivers agreed on a diagnosis of growth hormone insufficiency, only 39% stated receiving therapy.[3]
- In terms of peer relationships, their findings showed that youth with CP had significantly lower quality peer relationships, with a mean score from the current cohort one standard deviation lower than the mean for normative samples and previously released data for survivors of other childhood brain tumors.[3]
- Sterkenburg et al. findings indicate an OS of 88% of all CP patients.[4] However, they found that patients with HI had a considerably reduced OS rate (84% contrary to 95% in individuals without HI), and a more severe score in psychosocial parameters, severe QoL compromising outcomes, and other pathological sequelae.[4] Their findings supported the link between HI and extreme obesity.
- Interestingly, despite stabilization, the median BMI in individuals with HO over twelve years of monitoring was significant at +5.0 BMI SDS (Standard Deviation of the Samples).[4]

Risk Factors of HO

- Haliloglu et al.'s retrospective investigation saw BMI climb substantially in the first six months after therapy, then stabilized in all participants except the four who died. The total mortality risk was much greater among the current study's individuals who continued to gain weight after six months of therapy.[5]
- Participants aged less than six years at their time of diagnosis experienced higher all-cause and obesity-related mortality rates, and substantially higher 0-6 months post-treatment BMI SDS and maximal BMI SDS.
- The other distinctive observation was that participants with a maximum BMI SDS of three or higher at any point during the first three years following tumor treatment had a higher mortality risk. After tumor treatment, 95% of the participants in the current research exhibited more than one hormone deficit.[5]
- Growth hormone replacement medication was the only one that resulted in a reduction in BMI SDS six months after starting, and it was not related to an increase in the risk of death.[5]
- Schaik et al. retrospective study linked REE measurement outcomes to the clinical severity of HD and radiological posterior HD in this population. A few of the children who were clinically or radiologically suspected of having HD have REE measurement outcomes that are comparable to age and gender-related anticipated values.[6]
- There was a link between posterior HD and the Mueller grading, mammary body injury, endocrine dysfunction, clinical hypothalamic dysfunction, and low REE. Furthermore, not all children suspected of having HD have a low REE.[6]
- Jung et al. found that overall variability was adversely related to HI grade rather than central obesity, and the interaction effect of HI grade and central obesity on overall variability was not substantial. In conclusion, the lower HRV in individuals with more extensive HO implies that HD may play a role in cardiac autonomic dysfunction and emphasizes the necessity of limiting HD following childhood-onset CP.[7]

Treatment for HO

- Schaik et al.'s retrospective cohort discovered that dextroamphetamine therapy improved BMI in 82.4% of children with HO.[8] 76.5% of the children expressed an improvement in hyperphagia, behavior, and/or energy level.[8]
- The largest response was reported in the first six months of therapy for those who responded with a BMI decrease.[8] A rise in REE of more than 10% was seen in 62.5% of the patients who reacted with a BMI drop.[8] However, there were two non-responders with acquired HO with higher REE but with no positive influence on BMI.[8]
- Shoemaker et al. conducted a randomized, multicenter, double-blind placebo-controlled clinical that had no significant difference in weight change between groups for body composition. However, fat mass was not developing as fast in the ExQW group. The decrease in energy expenditure was comparable to the projected decline in energy intake by the ExQW group, resulting in no observed weight loss.[9]
- The ExQW group had reductions across all macronutrients, but the only significant treatment effect was the rise in the CEBQ score for eating slowness.[9] This group reported more fullness, but it was not statistically significant.
- McCormack et al performed a randomized, double-blind, placebo-controlled, crossover pilot clinical trial. The study's one significant weight loss began to lose weight near the conclusion of the placebo treatment, throughout the washout period, and while on OXT. There was no impact of OXT on BMI, BMI Z-score, or waist circumference.[10]
- However, those with HO had extended QTc intervals even before receiving OXT or a placebo. There was no effect of intranasal OXT on eating behaviors.[10]
- The research discovered a 10% drop in self-reported anxiety in the OXT-treated group but no rise in behavioral aggression or irritability attributed to this dosage of OXT. Moreover, the OXT resulted in faster suppression of undesirable responses/impulses.[10]

Limitations

- In terms of the goal of this review of literature, the relevant articles were limited.
- The limitations of each individual study may be due to sample size, lack of demographic information, predictive equations, study design, measures, selection bias, and more may explain why there is limited literature on this condition.
- Due to possible danger to children, permitting them to participate in scientific studies raises moral concerns. As a result, some of the articles cited had small sample sizes to be relevant to all children with HO, particularly those of different races or ethnicities.

Implications

- HO affects more than just physical health and emphasizes the need for a qualified dietitian's expertise in the care plan. Additionally, it can be observed that the risk factors for HO grow as the level of HI increases.
- An increase in low REE, increased fat mass, BMI, central obesity, and mortality risk. Because not all children are impacted in the same manner, a registered dietitian must interact with other healthcare experts to identify how they can individualize the care plan.
- There was a lot of variation in HO therapy and data showed that different medications are required to help treat HO weight gain and other variables that it negatively affects. Because modifying diet and physical activity are insufficient this research may require licensed dietitians to rethink how they conduct nutrition education counseling sessions.
- Moreover, raising awareness about the relevance of HO can benefit future research on how to enhance health outcomes and lower mortality risk in such individuals.

Conclusion

- The purpose of this review was to determine how HO impacts childhood development, HO risk factors, and prospective HO treatment approaches.
- Research on HO and how it impacts childhood development shows the obstacles that patients experience and the negative impact on survival rate, weight development, cognitive status, psychosocial status, and QoL.
- It raises the risk factors for HO as well as the comorbidities that arise because of it. Therefore, even with a change in diet and physical activity, the chance of mortality rises.
- The dextroamphetamine treatment influenced BMI and other HO-related parameters, but the effects subsided after some time. The GLP1RA therapy reduces calorie intake while decreasing energy expenditure. There was no effect on body weight or metabolic parameters with oxytocin, however, there was an effect on mood.
- Finally, additional research is required to discover which combination of therapies would be most successful, as well as to develop appropriate dietary and behavioral measures for this population.

Figure 1. Family dinner.[11]

Figure 2. Dance recital.[12]

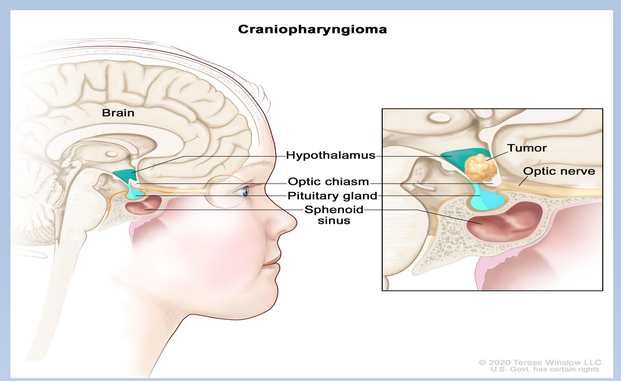

Figure 3. Childhood craniopharyngioma treatment (PDQ)- patient version.[13]

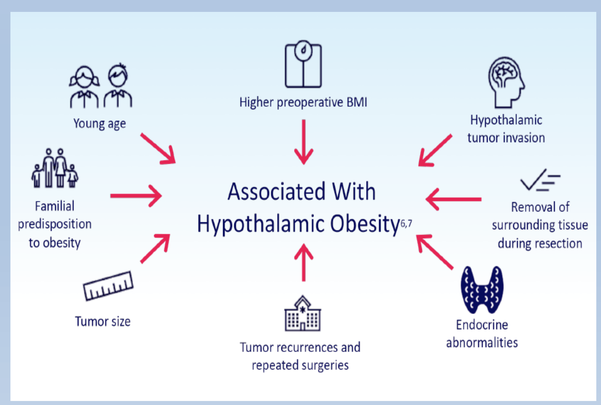

Figure 4. Hypothalamic Obesity.[14]

References

1. Erfurth, EM. Diagnosis, background, and treatment of hypothalamic damage in craniopharyngioma. J Neuroendocrinol. 2020;110-767-779. doi: 10.1159/000509616 2. Roth CL. Hypothalamic obesity in craniopharyngioma patients: disturbed energy homeostasis related to extent of hypothalamic damage and its implication for obesity intervention. J Clin Med. 2015;4:1774-1797. doi: 10.3390/jcm4091774 3. Craven M, Crowley JH, Chiang L, Kline C, Malbari F, Hocking MC, McCormack SE. A survey of patient-relevant outcomes in pediatric craniopharyngioma: focus on hypothalamic obesity. Front Endocrinol. 2022;13:876770. doi10.3389/fendo.2022.876770 4. Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbuchel AMM, Muller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. Neuro Oncol. 2015;17(7):1029-1038. doi: 10.1093/neuonc/nov044 5. Haliloglu B, Atay Z, Guran T, Abali S, Bas S, Turan S, Bereket A. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumors. Pediatr Obes. 2015;11:383-388. doi: 10.1111/ijpo.12076 6. Schaik JV, Burghard M, Lequin MH, et al. Resting energy expenditure in children at risk of hypothalamic dysfunction. Endocr Connect. 2022;11(8): e220276. doi: 10.1530/EC-22-0276 7. Jung HW, Kim HY, Kim JY, Cheon JE, Kim IO, Kim SK, Shin CH, Yang SW, Lee YA. Cardiac autonomic dysfunction is associated with hypothalamic damage in patients with childhood-onset craniopharyngioma. PLoS One. 2021;16(2): e0246788. doi. 10.1371/ journal.pone.0246789 8. Schaik JV, Welling MS, de Groot CJ, et al. Dextroamphetamine treatment in children with hypothalamic obesity. Front Endocrinol. 2022;13;845937. doi: 10.3389/fendo.2022. 845937 9. Shoemaker AH, Silver HJ, Buchowski M, Slaughter JC, Yanovski JA, Elfers C, Roth CL, Abuzzahab JM. Energy balance in hypothalamic obesity in response to treatment with a once-weekly GLP-1 receptor agonist. Int J Obes. 2022;46:623-629. doi: 10.1038/s41366-021-01043-6 10. McCormack SE, Wang Z, Wade KL, et al. A pilot randomized clinical trial of intranasal oxytocin to promote weight loss in individuals with hypothalamic obesity. J Endocr Soc. 2023;7:1-16. doi:10.1210/jendso/bvad037 11. Nesbitt A. Family Dinner. iPhone. Accessed March 19, 2024. 12. Nesbitt A. Dance Recital. iPhone. Accessed March 19, 2024. 13. National Cancer Institute. Childhood craniopharyngioma treatment (PDQ)- patient version. National Cancer Institute website. Updated September 07, 2023. Accessed March 19, 2024. https://www.cancer.gov/types/brain/patient/child-cranio-treatment-pdq 14. Rhythm Pharmaceuticals. Hypothalamic Obesity. Rhythm Pharmaceuticals website. Accessed March 19, 2024. https://www.rhythmmedicalgateway.com/hypothalamic-obesity.html