CASE REPORT

Distal gastric bypass surgery for the treatment of hypothalamic obesity after childhood craniopharyngioma

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Abstract

Context: Obesity resulting from damage to the hypothalamus, i.e. hypothalamic obesity, is a severe condition that currently lacks any effective evidence-based therapy.

Objective: Our goal was to describe the course of hypothalamic obesity in a craniopharyngioma patient treated with distal gastric bypass surgery and to outline distinct aspects of multidisciplinary case management.

Patient and methods: A 29-year-old man, who had undergone craniopharyngioma resection at the age of 8, was referred to our Interdisciplinary Obesity Centre with a body mass index (BMI) of 52.0 kg/m², type 2 diabetes and obstructive sleep apnoea syndrome (OSAS). After careful preoperative preparation, including the adjustment of hormone substitution therapy for panhypopituitarism, nutritional counselling and a supervised exercise program, he underwent a distal gastric bypass operation.

Results: Eighteen months after the operation the patient's BMI had decreased to 31.9 kg/m², type 2 diabetes was in complete remission, and OSAS appeared to be improved. Also, feelings of hunger were markedly reduced after the operation. A standard regimen of supplements successfully prevented any severe nutritional deficiencies. After weight loss, the dose of hydrocortisone could be distinctly reduced without any signs of adrenal insufficiency while GH substitution had to be markedly increased to achieve normal IGF1 levels.

Conclusions: Our case demonstrates that within a multidisciplinary team approach, a distal gastric bypass operation can be a safe and highly effective therapy for patients with hypothalamic obesity. Also, our findings hint at an effect of gastric bypass surgery on hunger and eating behaviour that may not essentially rely on hypothalamic mechanisms.

European Journal of Endocrinology 161 201–206

Introduction

Craniopharyngiomas are the most common tumours of the hypothalamic–pituitary region in children (1). After resection of the tumour, patients frequently display panhypopituitarism, which requires lifelong hormone replacement and, ~50% of cases, additionally suffer from obesity (2, 3) that is assumed to stem from damage to the ventromedial hypothalamus (VMH) (4). Dysfunctions of the VMH, which represent a key structure in the central nervous regulation of energy homeostasis and food intake (5), have been suggested to result in continuous hyperphagia (6). Alternatively, impaired VMH inhibition of efferent vagal nerve output to pancreatic β -cells may enhance insulin secretion (4) and thus induce a chronic anabolic state (7, 8). Supporting the latter assumption, a double-blind, placebo-controlled trial has shown that octreotide therapy, which ameliorates β -cell insulin secretion, reduces weight gain in non-diabetic children and adolescents with hypothalamic obesity (4). However, octreotide treatment cannot be administered to patients

already displaying type 2 diabetes mellitus because it would impair glycemic control. Also, given the moderate sized effect in relation to body weight, octreotide therapy would certainly be ineffective in the treatment of severe, also called morbid obesity (i.e. body mass index (BMI) > 40 kg/m²).

Bariatric surgery has been proven to be the most effective therapy for severe obesity (9). In addition to its body weight reducing effect it markedly reduces morbidity and mortality (10–13) and improves the quality of life (14). In this background, bariatric surgery may also be a therapeutic option for craniopharyngioma patients suffering from severe hypothalamic obesity. However, to the best of our knowledge, to date only one case report has been published which reported a 14-year old boy treated with a Roux-en-Y gastric bypass (15), the most frequently performed bariatric operation worldwide (16). Here, we report on a case of severe hypothalamic obesity in a craniopharyngioma patient that was successfully treated with a distal gastric bypass operation (17), i.e. another type of bariatric operation.

Case report

In September 2006, a 29-year-old man first presented to the Interdisciplinary Obesity Centre (IOC) for the evaluation of treatment options for his severe obesity (height: 1.77 m; weight: 163 kg; BMI: 52.0 kg/m²). At the age of 8 years, i.e. in 1985, the patient had undergone resection of a craniopharyngioma. A follow-up magnetic resonance imaging (MRI) of the brain performed in 2006 (Fig. 1) revealed no evidence for any recurrence of the tumour but showed a complete atrophy of the hypothalamus, suggesting a high risk of hypothalamic obesity. Available clinical reports dating back to July 1997 documented a progressive increase in body weight and BMI up to the age of 24 (i.e. 2001). In April 2001, type 2 diabetes was diagnosed and metformin therapy was introduced (Fig. 2). Nateglinide was added in November 2005. At the first presentation in the IOC the patient showed good glycemic control (fasting glucose: 6.8 mmol/l; HbA1c 5.8%) under a dose regimen of 3400 mg metformin and 120 mg nateglinide every day. Also, obstructive sleep apnoea syndrome (OSAS) had been treated with nasal continuous positive airways pressure (nCPAP) since 1995. As documented in several clinical reports, the patient had to be repeatedly hospitalized for the antibiotic treatment of erysipelas of the lower limbs.

At the first presentation in the IOC, blood pressure was normal (118/80 mmHg) and the lipid profile was only moderately altered (triglycerides: 2.8 mmol/l, total cholesterol: 4.3 mmol/l, low density lipoprotein: 2.1 mmol/l, high density lipoprotein: 0.9 mmol/l). Elevated fasting glucose (6.8 mmol/l) in conjunction with elevated insulin (11.0 mU/l; normal range: <10 mU/l) and C-peptide (1525 pmol/l; normal range: 320–780 pmol/l) levels pointed to a state of moderate

Figure 1 Cranial magnetic resonance images 21 years after resection of a craniopharyngioma. Right image: non-enhanced, coronal, T1 weighted. Left image: contrast-enhanced, sagittal, T1 weighted. Thick arrows, excavation of the sella turcica; dashed arrow, tuber cinereum with atrophy of the hypothalamus; solid thin arrow, missing floor of third ventricle.

Figure 2 Development of the patient's BMI. Born in 1977, the patient underwent resection of a craniopharyngioma in 1985.

insulin resistance (homeostasis model assessment–insulin resistance (18): 3.3). Indirect calorimetry (Deltatrac II, TM MBM 200, Hoyer, Bremen, Germany) revealed a resting energy expenditure (REE) of 3280 kcal/24 h which was about 10–17% higher than the expected REE calculated by established formulas (Müller *et al.* (19): 2801 kcal/24 h; Harris & Benedict (20): 2996 kcal/24 h). Bioelectrical impedance analysis (Akern RJL101S, Akern, Pontassieve, Italy) revealed a body fat mass of 52 kg, i.e. 31.8% of body weight. A cardiopulmonary exercise test revealed a $\text{VO}_{2\text{peak}}$ of 2.41 l/min corresponding to 200 W and a peak heart rate of 143 min.

Due to panhypopituitarism as a consequence of craniopharyngioma resection, the patient continuously received hormone replacement therapy before and after the bariatric operation as listed in Table 1. As the patient showed massive oedema of the lower limbs at the first presentation the dose of intranasal (i.n.) desmopressin was reduced in a stepwise fashion prior to the bariatric operation (from 60 to 10 µg/day i.n.) as was the dose of hydrocortisone (from 40 to 30 mg/day per os (p.o)). Since the patient reported on alterations and fluctuations in mood, the testosterone replacement therapy was switched from i.m. injections of 250 mg every third week to a daily transdermal application of 50 mg testosterone. Although the insulin-like growth factor-1 (IGF1) level (15.4 nmol/l) was only at the lower limit of the age-related normal range (15.2–42.8 nmol/l) the GH substitution dose (0.3 mg/day) was not increased. Based on the good glycaemic control, nateglinide was stopped and the metformin dose was reduced to 2000 g/day. In order to induce preoperative weight loss, the patient received 15 mg sibutramine in addition to dietary counselling and physical exercise (performed under the supervision of the IOC physiotherapeutic staff). Reflecting the effectiveness of these measures as

Table 1 Hormone substitution therapy before and after the distal gastric bypass operation.

	First presentation	Immediately pre-OP	1-year post-OP	1.5-years post-OP
Hydrocortisone (mg)	40 p.o./day	30 p.o./day	20 p.o./day	10–15 p.o./day
Levothyroxin (µg)	250 p.o./day	250 p.o./day	250 p.o./day	250 p.o./day
Testosterone (mg)	250 i.m. every 3 weeks	50 t.d./day	50 t.d./day	50 t.d./day
GH (mg)	0.3 s.c./day	0.3 s.c./day	1.2 s.c./day	1.2 s.c./day
Desmopressin (µg)	60 i.n./day	10 i.n./day	10 i.n./day	10 i.n./day

t.d., transdermal; i.n., intranasal; i.m., intramuscular; p.o., per os; s.c., subcutaneously.

well as the high motivation of the patient his body weight decreased by 11 kg from the time of the first presentation (163 kg) to the operation (152 kg).

In June 2007, the patient underwent a distal gastric bypass operation with a common channel of 80 cm, a biliopancreatic limb of 80 cm and an alimentary limb of 780 cm in combination with a cholecystectomy. This type of operation was chosen since we expected the patient to require a rather strong malabsorption, especially of nutritional fat, to achieve a good weight loss result. This expectation was based on the following considerations: given the extended hypothalamic lesion, we expected the patient to display enhanced feelings of hunger. In fact, the three factor eating questionnaire (TFEQ (21)) had rather shown a high level of restraint eating (10 out of 21) in conjunction with moderate levels of disinhibition (8 out of 16), but strong feelings of hunger (8 out of 14). The standard proximal gastric bypass operation, which does not exert strong malabsorptive effects, has been shown to alter gut hormone release, e.g. to reduce ghrelin secretion (22–25) and enhance secretion of glucagon-like-peptide (GLP)-1 and PYY (22, 23), that putatively favours feelings of satiety and reduces hunger. Because these hormonal alterations are currently hypothesized to mainly exert their influence on eating behaviour via hypothalamic mechanisms (26), they were expected to be less effective in a patient with a profoundly damaged hypothalamus. Contrasting this assumption, Inge *et al.* (15) have reported on markedly diminished food craving in their adolescent craniopharyngioma patient after standard proximal gastric bypass surgery (15). While this beneficial effect could in principle have been mediated by non-hypothalamic mechanisms, it could also have resulted from a rather restricted damage to the ventromedial hypothalamic region that probably left intact other hypothalamic key structures such as the arcuate nucleus (ARC). While the cranial MRI of our patient did not allow us to discriminate damages to distinct hypothalamic structures, preservation of relevant nuclei such as the ARC or the lateral hypothalamus overall appeared rather unlikely. It should also be noted that the adolescent patient of Inge *et al.* (15) showed an impressive ~22% weight loss along with a marked improvement of metabolic features, but the patient's BMI remained very high (> 50 kg/m²) even 2.5 years after the operation. Taken

together, in our patient we assumed the influence of hormonal alterations after a gastric bypass operation on hunger and appetite to be rather mild and maybe insufficient to achieve a satisfactory weight loss. Therefore, the induction of a strong malabsorptive component by means of a distal gastric bypass with a distinctly shortened common channel (i.e. the distance from the Roux-en-Y enteroenterostomy to the ileocecal junction) was deemed necessary. Our decision to perform a distal gastric bypass operation was also guided by previous results from Brolin *et al.* (17) showing a reduction of body weight greater after distal than proximal gastric bypass surgery, especially in patients with a BMI above 50 kg/m².

The operation was performed laparoscopically without any complication and the patient was discharged from the hospital on the eighth postoperative day. During the first three postoperative months, he lost 34 kg body weight (152–118 kg) and a further 8 kg respectively, during the fourth to sixth (to 110 kg) and the seventh to eighth postoperative month (to 102 kg) with an additional loss of 4 kg from the ninth to the twelfth postoperative month (to 98 kg). From the thirteenth to the eighteenth postoperative month he regained 2 kg (to 100 kg). Eighteen months after the operation, body fat had dropped to 27 kg (27% of body weight) and REE had decreased to 2510 kcal/day which is 28–29% higher than the expected values (Müller *et al.* (19): 1778 kcal/24 h; Harris & Benedict (20): 1810 kcal/24 h). Spiroergometry, also performed 18 months after the operation, revealed a reduced VO_{2 peak} of 1.90 l/min as compared with the preoperative state (i.e. 2.41 l/min) but an identical power output (200 W) and peak heart rate (142 min).

To prevent nutritional deficiencies, a standard supplementation therapy regimen including 100 mg iron/day p.o., 30 mg zinc/day p.o., 1.5 g calcium/day p.o., 1500 IU vitamin D₃/day p.o., one multivitamin pill containing trace elements/day, and one tablet of vitamin B-complex (twice a week) was prescribed to the patient. In addition, 1000 IU vitamin B₁₂ was injected i.m. every 3 months. The baseline and follow-up nutritional measurements are listed in Table 2.

Regarding comorbidities, metformin therapy could be stopped immediately after operation without any alteration in glycemic control, indicating a complete resolution of type 2 diabetes. Also, after sleeping more

Table 2 Relevant blood measurements before and after the distal gastric bypass operation.

	Pre-OP	3 months post-OP	6 months post-OP	10 months post-OP	12 months post-OP	15 months post-OP	18 months post-OP	Reference range
Haemoglobin (g/dl)	149.0	144.0	138.1	131.0	136.0	131.0	144.0	140.0–180.0
Total protein (g/l)	71	73	68	65	65	66	62	63–83
Albumin (μ mol/l)	656	678	654	603	580	565	572	493–696
Sodium (mmol/l)	135	138	136	135	140	135	129	130–145
Total calcium (mmol/l)	2.3	2.4	2.3	2.3	2.3	2.2	2.2	2.0–2.5
iPTH (pmol/l)	2.6	2.2	3.1	2.1	1.6	2.5	2.2	1.5–6.5
25(OH)D ₃ (nmol/l)	64	91	36	22	123	54	30	76–250
Vitamin B ₁₂ (pmol/l)	150	246	244	124	113	179	272	133–664
Folic acid (nmol/l)	17.5	44.0	36.0	38.5	36.5	23.6	10.8	4.5–27.2
Ferritin (pmol/l)	300	431	298	369	273	325	252	46–600
Zinc (μ mol/l)	16.4	13.2	9.6	12.4	18.1	10.1	17.6	11–18
Fasting glucose (mmol/l)	6.8	4.5	5.0	5.3	4.0	4.4	4.5	3.9–6.0
Insulin (pmol/l)	76	—	—	—	30	—	54	<70
HOMA-IR	3.3	—	—	—	0.8	—	1.6	≤ 1
C-peptide (pmol/l)	1525	—	—	—	493	—	—	320–780
HbA1c (%)	5.8	4.1	—	—	4.2	—	4.3	4.3–5.8
Triglyceride (mmol/l)	2.8	1.3	1.3	1.5	1.9	1.2	1.8	<1.7
Total cholesterol (mmol/l)	4.3	2.7	2.5	2.5	3.0	2.9	2.9	<5.0
LDL-cholesterol (mmol/l)	2.1	1.1	0.9	0.8	0.6	1.0	1.0	<2.6
HDL-cholesterol (mmol/l)	0.9	1.0	1.0	1.0	1.5	1.4	1.1	>1.0

than 10 years with a nCPAP device the patient stopped this therapy since he believed that he did not benefit from it any longer. Accordingly, overnight pulse oximetry revealed no desaturation below 90% and an average saturation of 99.4% (total recording time 7 h 18 min), suggesting an improvement or even resolution of OSAS.

As listed in Table 1, the hydrocortisone substitution dose could be reduced to 10–15 mg per day without occurrence of any syndrome of adrenal insufficiency. The levothyroxin dose did not change over time. Interestingly, the GH dose had to be markedly increased (to 1.2 mg/day) to achieve an IGF1 level (23.3 nmol/l) within the age-related normal range (15.0–40.0 nmol/l). Overall, the patient was highly satisfied with the success of the bariatric operation and reported on a significant improvement of his quality of life. Interestingly, the TFEQ applied 18 months after operation indicated a distinct reduction of feelings of hunger (2) and disinhibition (4), while the level of cognitive restraint (11) slightly increased (preoperative values: 8, 8 and 10 respectively).

Discussion

Our case demonstrates that distal gastric bypass surgery can be a safe and effective therapy for patients with severe hypothalamic obesity after resection of childhood craniopharyngioma. In our patient, weight loss following the operation was significant and associated with a marked improvement of severe comorbidities, i.e. a resolution of type 2 diabetes and a clinical improvement of OSAS. Also, quality of life, as clearly stated by the patient, significantly improved after the bariatric operation. However, our follow-up period of

only 1.5 years precludes any conclusions regarding the long-term effects of a distal gastric bypass operation in such patients.

Hypothalamic obesity resulting from damage to hypothalamic brain structures is a frequent complication of craniopharyngioma treatment that currently lacks an effective therapy (27). While octreotide treatment appears to diminish weight gain, a significant reduction of body weight is hardly achieved by this pharmacological therapy (4). Also, other kinds of pharmacological approaches, e.g. using adrenergic or serotonergic agents, have yielded rather disappointing results (28). However, even in severely obese subjects without any hypothalamic lesion, i.e. non-hypothalamic obesity, long-term weight reduction is difficult to achieve by pharmacologic, dietary and behavioural interventions, so that bariatric surgery currently represents only effective therapy for such patients (29). The question arises of whether bariatric surgery is also an effective and safe therapeutic option in patients with hypothalamic obesity. Inge *et al.* (15) have previously reported on the successful treatment of a 14-year old boy with hypothalamic obesity occurring after surgical resection and radiotherapy of a craniopharyngioma by a proximal gastric bypass operation (15). As in our patient, OSAS markedly improved and insulin levels decreased after surgery and no severe adverse side effects were observed over a follow-up period of 2.5 years. Of note, the patient of Inge *et al.* lost ~22% body weight, whereas our patient lost ~39% of his initial body weight (i.e. ~35% of the body weight immediately before the operation). Thus, our patient reached a BMI of 32.9 kg/m², whereas the BMI of the former patient clearly remained above 50 kg/m². Although the difference in absolute weight loss appears to be less impressive (63 and 53 kg

respectively, versus 49 kg), this pattern of results supports our initial assumption that in massively obese patients (BMI > 50 kg/m²) without hypothalamic lesions, distal gastric bypass surgery elicits a greater weight loss than standard proximal gastric bypass procedures (17).

Potential nutritional deficiencies represent one of the most challenging concerns in bariatric surgery (30). While severe nutritional deficiencies could be prevented in our patient by a standardized supplementation regime, laboratory analysis still revealed slight and transitory alterations. For instance, discrete anaemia was observed between the ninth and fifteenth post-operative month and suboptimal 25-hydroxyvitamin D₃ levels were repeatedly observed during the 1.5-years follow-up. Also, serum levels of zinc and vitamin B12 were repeatedly found to be slightly reduced. Total protein as well as albumin appeared to decrease over time and total protein concentration even fell below the lower limit of the reference range 18 months after the operation. Hypoproteinemia is of particular relevance after distal gastric bypass operations (17) since the short common channel may not only limit absorption of nutritional fat but also protein uptake. Taken together, our results clearly underline the necessity of structured follow-up programs and lifelong supplementation regimes for patients undergoing distal gastric bypass operations.

In addition to the impressive improvement of metabolic features and to the observed nutritional challenges after the operation, several other aspects of this case deserve to be highlighted. First, in order to reduce body weight we preoperatively prescribed sibutramine to the patient which resulted in an impressive weight loss of 11 kg over a 6 month period. While this weight loss may not be solely attributable to sibutramine given that nutritional counselling, supervised exercise, and the reduction of hydrocortisone and desmopressin doses most likely also contributed to weight loss, we felt that the medication worked quite well in our patient. Clearly, this observation deserves further and more systematic investigation.

Another remarkable observation is that the patient, contrary to our expectations of only mild effects on the motivation to eat, reported greatly reduced feelings of hunger – as reflected by the result on the TFEQ – and also reduced food craving and disinhibition after the operation. This finding suggests that the distal gastric bypass operation affects central nervous processes that do not solely rely on hypothalamic structures but also involve higher brain centres. However, it should be emphasized that although the patient's MRI showed a complete atrophy of the hypothalamus, a preservation of functionally intact hypothalamic structures cannot be excluded. Also, whether the effects on eating behaviour are triggered by changes in gastrointestinal hormone secretion – that have not been assessed here – remains to be explored. Previous studies on gastric

bypass surgery have demonstrated an enhanced postprandial response of the satiety hormones GLP-1 and PYY (23) while circulating levels of the hunger-promoting hormone ghrelin were found to be reduced (24). It seems reasonable to assume that these hormonal changes observed after gastric bypass surgery are likewise present in patients with hypothalamic obesity. In fact, Inge *et al.* have reported on a marked reduction of active ghrelin levels in their craniopharyngioma patient after the operation (15). Considering that ghrelin-responsive neuronal circuits exist in brainstem (31) and midbrain (32), post-operative changes in the concentration of this hormone could, in theory, contribute to effects of the gastric bypass surgery on eating behaviour that presumably do not rely exclusively on hypothalamic mechanisms.

Although the postoperative course of our patient was very impressive and obviously successful, there are some caveats regarding the extrapolation of this observation to comparable patients. Our patient was highly selected as he had to demonstrate a high level of motivation and compliance, regarding, for example, pre-operative weight loss, exercise and regular visits at our IOC, before we made the decision to offer him operation. Also, the refined peri-operative management of the patient clearly required a multidisciplinary team that may not be available at every institution performing bariatric operations. While overall, we strongly encourage surgeons as well as endocrinologists and probably also paediatricians who are confronted with comparable patients suffering from hypothalamic obesity to consider a bariatric operation, we also recommend them to be very careful in the selection of potential candidates and to provide a sustained peri-operative management to such patients. Finally, the risks of nutritional deficiencies along with potential supplementation requirements as well as the burden of lifelong follow-up examinations need to be considered. However, all these risks and efforts must be balanced against the lack of any other effective therapy and the cost of otherwise untreatable massive obesity.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or non-profit sector.

Acknowledgements

We thank the patient for giving us the permission to publish his case. Also, we thank all members of the IOC team and the Kantonsspital St Gallen who helped in managing and taking care of the patient.

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Received 27 March 2009

Accepted 28 April 2009