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Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours

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Summary

Background: Hypothalamic obesity (HyOb) is a common complication of childhood hypothalamic tumours. Patients with HyOb probably have a higher mortality rate than those with other types of obesity due in many cases to obstructive sleep apnoea/hypoventilation.

Objectives: To identify predictive factors for mortality caused by HyOb in children.

Methods: Twenty children with HyOb secondary to hypothalamic tumours that were followed-up for ≥3 years and aged <15 years at diagnosis, and received supraphysiological glucocorticoid treatment for ≤1 month.

Results: Mean age at diagnosis was 6.36 ± 3.60 years. Mean body mass index (BMI) Standard deviation of the samples (SDS) increased from 0.77 ± 1.26 to 2.66 ± 1.45 during the first 6 months, but slowed from month 6–12 (2.73 ± 1.35). ΔBMI SDS at 0–6 months was significantly higher in patients aged <6 years at diagnosis than in those aged >6 years at diagnosis (3.71 ± 1.96 vs. 0.83 ± 0.73, $P < 0.001$). Maximum BMI SDS was also significantly higher in the younger group (3.88 ± 1.39 vs. 2.79 ± 0.64, $P < 0.05$). In all, four patients died and the mortality rate was significantly higher in the patients with a further increase in BMI SDS > 1 SDS after 6 months of therapy (RR: 8.4, $P < 0.05$). Both overall mortality and obesity-related mortality rates were higher in the patients aged <6 years at diagnosis (4.5-fold, 7.2-fold higher, respectively, $P > 0.05$). The mortality rate was also 3.7-fold higher in the patients with a maximum BMI SDS ≥ 3 at any time during the first 3 years after therapy($P > 0.05$).

Conclusions: An increase in BMI SDS after 6 months of therapy was observed to be a risk factor for mortality caused by HyOb. In addition, age <6 years at diagnosis and a maximum BMI SDS ≥ 3 were associated with a higher mortality rate, indicating that earlier and more aggressive treatment of obesity is required.

Keywords: Brain tumour, craniopharyngioma, mortality.

Introduction

Hypothalamic obesity (HyOb) is a complex neuroendocrine disorder caused by damage to the hypothalamus. HyOb causes rapid, unrelenting and intractable weight gain that is not responsive to diet or lifestyle modifications, and results in significant morbidity and mortality (1). Children with brain tumours are at high risk for the development of HyOb, either related to tumour treatment or the tumour itself. Management of patients with suprasellar brain tumours requires a multidisciplinary approach due to a high morbidity and mortality risk independent of disease progression (2–4). The best-known and most extensively documented cause of HyOb in patients with brain tumours is craniopharyngioma (CP). Chronic hypothalamic insufficiency, cerebrovascular disease, hormonal deficiencies, and cardiovascular diseases are causes of late mortality in patients with CP (2,4). HyOb also contributes to this process and increases the risk of mortality.

Sleep disorders are common in patients with CP and are associated with the severity of obesity (2). Although some predictive factors for the development of HyOb have been described, such as tumour localization, histology, radiotherapy and hypothalamic endocrinopathy (5), the risk factors for mortality caused by HyOb in children remain unknown. The present study aimed to identify the risk

Predictive factors for the development of hypothalamic obesity (HyOb) are already known.
Predictive factors for mortality caused by HyOb are lacking and this study identified such risk factors.

factors for the severity of HyOb and mortality due to HyOb in children.

Methods

This retrospective study analysed 135 children with primary brain tumours that were followed-up between 2000 and 2013 at Marmara University Hospital, Department of Pediatric Endocrinology, Istanbul, Turkey. Among the 78 subjects with hypothalamic involvement, 45 were regularly followed-up. Obesity was noted in 24 of these 45 subjects, of which 20 fulfilled this study's inclusion criteria, which were body mass index (BMI) SDS ≥2 at any time after tumour diagnosis, follow-up of ≥3 years after initial presentation with brain tumour, and supraphysiological glucocorticoid treatment (12 mg/m^2/d hydrocortisone equivalent) for ≤1 month (5). Age at diagnosis, height and weight at each follow-up visit, tumour location, tumour histology, treatment modalities (surgery, radiotherapy [RT], chemotherapy [ChT]), hypothalamic endocrinopathies, hormone replacement therapy and cause of mortality were recorded. BMI was calculated using the formula (weight [kg]/height [m^2]) and BMI SDS was obtained using growth charts specific for Turkish children (6). In addition, 21 non-obese children that were regularly followed-up were evaluated (Figure 1).

Statistical analysis was performed using Microsoft Excel program for Windows. The *t*-test was used to compare mean BMI SDS, according to subject age or hormone replacement status. Relative risk was calculated using chi-square contingency tables.

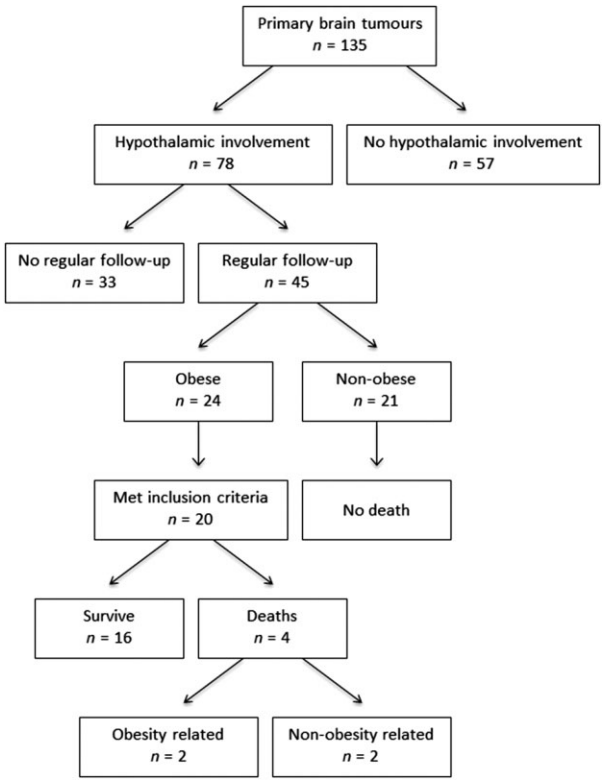

Figure 1 Study design.

Results

Of the 24 retrospectively analysed obese subjects, 20 were included the study. Mean age of the 20 subjects at initial presentation was 6.36 ± 3.60 years (range: 0.50–13.82 years), mean height SDS was –0.69 ± 1.46 (range: –3.69–1.61), mean weight SDS was 0.40 ± 1.65 (range: –2.51–2.70), and mean BMI SDS was 0.80 ± 1.25 (range: –1.74–2.55). Mean duration of follow-up was 6.02 ± 2.5 years (range: 3.3–11.9 years) and mean BMI SDS was 2.26 ± 1.42, 2.52 ± 1.09, 2.66 ± 1.41, 2.38 ± 1.21, 1.97 ± 1.27, and 1.69 ± 0.77 at 6 months, 1 year, 2 years, 3 years, 5 years and 7 years of follow-up, respectively (Fig. 2). All tumours were located in the thalamus or hypothalamus (suprasellar location). The most common tumour histopathology was optic glioma (*n* = 9 [45%]), followed by CP (*n* = 8 [40%]). Other causes were meningioma, histiocytosis and hamartoma (*n* = 3 [15%]). In all, two of the subjects were obese at diagnosis (one with optic glioma and one with hamartoma). Surgery was the first-line treatment in 18 subjects. ChT alone was used in one subject and RT was used in three subjects (RT+ChT: *n* = 1; S+RT: *n* = 1; S+RT+ChT: *n* = 1). Because of tumour recurrence, seven subjects underwent surgery two times and two underwent surgery three times.

In 15 of 20 subjects whose data were available for 0, 6 and 12 months post-treatment (S: *n* = 14; RT+ChT: *n* = 1) change in BMI SDS was calculated. In total, seven (47%) of these 15 subjects had CP and eight (53%) did not. Mean BMI SDS increased from 0.77 ± 1.26 to 2.66 ± 1.45 during the first 6 months post-treatment (*P* < 0.01) and ΔBMI SDS

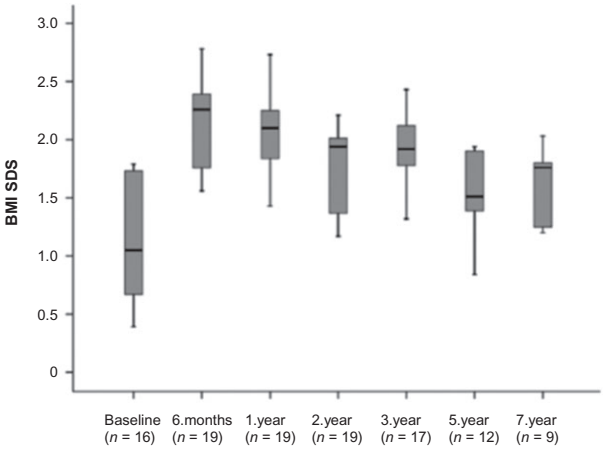

Figure 2 Mean BMI SDS during 7 years of follow-up in patients with hypothalamic obesity. The boxes represent interquartile range (25–75%), the horizontal lines in the boxes are median value, the ends of vertical lines represent minimum and maximum values except the extreme outliers.

Table 1 BMI SDS and ΔBMI SDS in non-obese subjects and according to age at diagnosis in subjects with HyOb

	Non-obese subjects	HyOb subjects ($n = 15$)*	Age at diagnosis (years)		
			≤6 ($n = 5$)	>6 ($n = 10$)	*P*
BMI SDS at diagnosis	–0.81 ± 1.58	0.77 ± 1.26	0.10 ± 1.63	1.14 ± 0.91	NS
BMI SDS at 6 months	–0.52 ± 1.53	2.66 ± 1.45	3.82 ± 1.86	2.02 ± 0.63	0.01
BMI SDS at 12 months	–0.71 ± 0.96	2.73 ± 1.35	3.78 ± 1.59	2.09 ± 0.61	<0.01
Max BMI SDS	0.24 ± 1.03	3.23 ± 1.12	3.88 ± 1.39	2.79 ± 0.64	<0.05
ΔBMI SDS at 0–6 months	0.39 ± 0.83	1.79 ± 1.85	3.71 ± 1.96	0.83 ± 0.73	<0.001
ΔBMI SDS at 6–12 months	–0.03 ± 1.39	0.04 ± 0.42	–0.04 ± 0.50	0.07 ± 0.38	NS
ΔBMI SDS 0-maxBMI SDS	0.99 ± 1.14	2.36 ± 1.78	3.81 ± 2.09	1.49 ± 0.80	<0.01
ΔBMI SDS 6-maxBMI SDS	0.73 ± 1.03	0.97 ± 1.81	2.00 ± 2.75	0.56 ± 0.67	<0.05

*In five subjects, the precise BMI at diagnosis was not known and they were excluded from this calculation.NS, not significant.

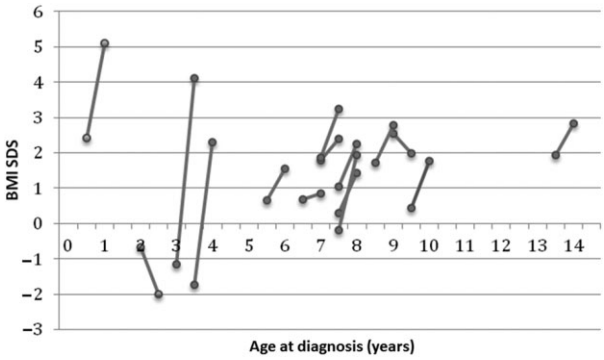

Figure 3 Individual changes in BMI SDS during the first 6 months following primary tumour therapy in 15 subjects with hypothalamic obesity.

Table 2 HyOb subjects with endocrinopathies and their treatment

	Total subjects (*n*)	Treated subjects (*n*)
GH deficiency	17	6
Central adrenal insufficiency	13	13
Central hypothyroidism	18	18
Diabetes insipidus	15	15
Gonadotropin deficiency	9	7
Precocious puberty*	3	3

*One subject with hamartoma developed precocious puberty prior to surgery and two others with optic glioma did not undergo surgery.

for 0–6 months was 1.79 ± 1.85. This rapid increase in BMI did not persist between 6 and 12 months post-treatment (BMI: 2.66 ± 1.45 to 2.73 ± 1.35; ΔBMI SDS: 0.04 ± 0.42). A significant difference was observed between ΔBMI SDS for 0–6 months and ΔBMI SDS for 6–12 months ($P < 0.01$; Table 1).

Subgroup analysis according to the age at diagnosis showed that mean ΔBMI SDS for 0–6 months post-treatment was significantly higher in subjects aged <6 years at diagnosis than in those aged >6 years at diagnosis ($P < 0.001$; Fig. 3). The mean maximum BMI SDS was also significantly higher in the aged <6 years at diagnosis subgroup (3.88 ± 1.39 vs. 2.79 ± 0.64, $P < 0.05$; Table 1). As the rate of increase in BMI slowed after 6 months post-treatment in all groups, we sought to determine if the increase in BMI SDS from 6 months to max BMI differed according to age at diagnosis, and it was observed the increase in BMI during this period was significantly higher in the aged <6 years at diagnosis subgroup ($P < 0.05$).

During follow-up multiple hypothalamic hormone deficiency developed in 17 subjects, two subjects developed isolated hypothyroidism with precocious puberty, and one subject did not develop any hormonal deficiency (Table 2). Growth hormone (GH) for ≥6 months was given to six subjects (CP: $n = 5$; optic glioma: $n = 1$). GH treatment was initiated 4.21 ± 2.91 years after tumour therapy. BMI SDS after 6 months of GH treatment decreased from 1.82 ± 0.64 to 1.47 ± 0.58 ($P < 0.05$) and ΔBMI SDS for 0–6 months of GH treatment was –0.35 ± 0.33. GH therapy was discontinued in two subjects because of tumour recurrence. None of the subjects that received GH therapy died. In addition, seven subjects that received sex steroid replacement because of hypogonadotropic hypogonadism were also analysed for change in BMI SDS and mean ΔBMI SDS for 0–6 months of sex steroid treatment was –0.04 ± 0.24 (1.48 ± 0.93 vs. 1.44 ± 0.93, $P = 0.32$).

In total, four subjects died during follow-up; two of the subjects' deaths were obesity related (hypoventilation at age 3.7 years and obstructive sleep apnoea at age 6 years) and two subjects (aged 7.1 years and 10.2 years) died because of complications during the early post-operative period (Fig. 4). The mortality rate was significantly higher in subjects with ΔBMI SDS from 6 months of therapy to maximum BMI >1 SDS (60% vs. 7.1%, RR: 8.4, $P < 0.05$). The mortality rate was 4.5-fold higher in the aged <6 years at diagnosis subgroup than in the aged >6 years at diagnosis subgroup (37.5% vs. 8.3%, $P > 0.05$). Moreover, the mortality rate was 3.7-fold higher in the subjects with a maximum BMI SDS ≥3 at any time during the first 3 years after tumour therapy (33.3% vs. 9%, $P > 0.05$; Fig. 5).

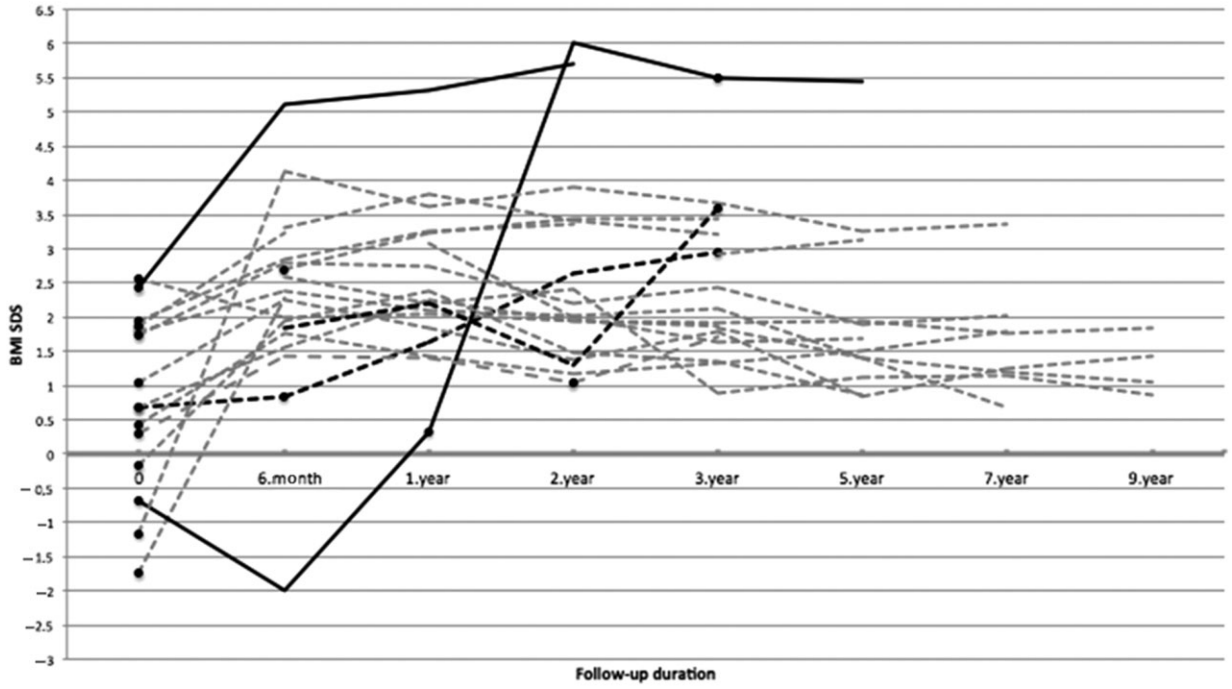

Figure 4 Individual changes in BMI SDS during 9 years of follow-up in patients with hypothalamic obesity. Black lines: obesity-related deaths. Black dashed lines: deaths related to post-operative complications. Grey dashed lines: alive patients. Black circles: time of operation.

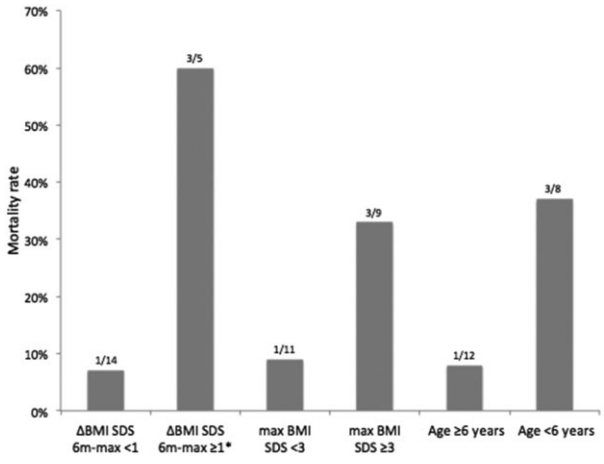

Figure 5 Mortality rates according to ΔBMI SDS (from BMI SDS at 6 months of therapy to maximum BMI SDS), maximum BMI SDS (the highest BMI SDS ever achieved during follow-up), and age at diagnosis. *: $p < 0.05$.

Evaluation of obesity-related mortality only showed that two such subjects were much younger (aged 0.6 and 2 years) than the others (median age: 7.28 years) at the time of diagnosis. The obesity-related mortality rate was 7.2-fold higher in the aged <6 years at diagnosis subgroup than in the aged >6 years at diagnosis subgroup. Furthermore, the two young outliers with obesity-related deaths gained considerably more weight than the others (max BMI SDS 5.71 and 6.01 vs. median BMI SDS 2.57, respectively; Fig. 4) and both had multiple pituitary hormone deficiencies.

The first case of obesity-related mortality was a boy that presented at age 2 years with optic glioma and diencephalic syndrome. The patient had failure to thrive at diagnosis and continued to lose weight after his first surgery. He subsequently developed central hypothyroidism and central diabetes insipidus; l-thyroxine and desmopressin were initiated. He developed central adrenal insufficiency after his second surgery and hydrocortisone was added to the treatment. Following the second operation, while receiving Ch+ RT at age 3 years and 9 months he began to gain weight and his BMI increased from 16 to 36 within 2 years. Interventions aimed at lifestyle modification failed and he died due to central hypoventilation syndrome at age 6 years.

The other case of obesity-related mortality presented at age 7 months with vaginal bleeding and gelastic seizures, and was diagnosed as hypothalamic hamartoma. Her BMI was 20.4 at diagnosis. She was treated with a GnRH analog for central precocious puberty. At age 2 years she underwent surgery due to refractory seizures. She developed central hypothyroidism, central adrenal insufficiency, central diabetes insipidus, hypodipsia, and weight gain following the operation. L-thyroxine, hydrocortisone and desmopressin replacement were initiated. She developed severe obesity within 3 months of surgery (BMI: 33.9; BMI SDS: 5.71). Attempts at lifestyle modification in this case also failed. A somatostatin analogue (octreotide) 5 μg/kg/d

was administered at 7 months post-surgery. The patient developed severe diarrhea during the third month of this treatment, and as a therapeutic dose could not be achieved octreotide was withdrawn. At age 3 years 9 months the patient was diagnosed as severe central apnoea syndrome based on polysomnography, but she died prior to initiation of non-invasive ventilation.

Mean age at diagnosis in 21 non-obese subjects was 7.13 ± 4.41 years (range: 1.12–15.01 years), of which 4 were aged <6 years and 11 (52%) were diagnosed as CP. Mean BMI SDS was –0.81 ± 1.58, –0.52 ± 1.53, –0.71 ± 0.96, –0.80 ± 1.5, –0.86 ± 1.64, –0.55 ± 2.00 and –0.09 ± 1.53 at initial presentation, 6 months, 1 year, 2 years, 3 years, 5 years and 7 years of follow-up, respectively. The increment in BMI SDS between 6 and 12 months post-treatment was not significant ($P = 0.30$; Table 1). None of the non-obese subjects died during follow-up.

Discussion

HyOb is the most frightening endocrinological problem following surgical intervention in children with brain tumours. HyOb responds poorly to conventional lifestyle modification and is usually resistant to pharmacological treatment (1). Although not precisely known, patients with HyOb probably have a higher mortality rate than patients with other types of obesity; therefore, its diagnosis and identification of the associated risk factors for mortality are important. The present study synopsized our single-centre experience with obesity-related mortality in children with HyOb. The two patients with obesity-related mortality were youngest and had the highest maximum BMI SDS.

In patients with CP, the frequency of severe obesity is as high as 55% and rapid weight gain occurs within the first 6–12 months following treatment (2,7,8). Similarly, in the present study BMI increased rapidly during the first 6 months post-treatment, followed by stabilization in all subjects, except the four that died. Also, this increment was not observed in non-obese subjects. These findings indicate that the first 6 months after tumour therapy is extremely critical for the prevention of severe HyOb. Additionally, overall mortality risk was significantly higher in the present study's subjects that continued to gain weight beyond 6 months post-treatment, which to the best of our knowledge has not been previously reported.

For subgroup analysis, age 6 years was chosen as the threshold because the physiological increase in BMI percentile begins after age 6 years in Turkish children (6), and earlier studies have used age 5–6 years as a cut-off for identifying risk factors for the development of HyOb (5,8). Furthermore, it was obvious that in the present study's cohort both all-cause and obesity-related mortality rates were higher in the subjects aged <6 years at the time of diagnosis and that they also had significantly higher 0–6 months post-treatment ΔBMI SDS and maximum BMI SDS ($P < 0.001$). Previous studies also reported that young age at diagnosis is a risk factor for HyOb (5,9); however, in addition to the risk of obesity, the present study shows for the first time that age <6 years at diagnosis is also associated with increased mortality in children with HyOb. The other novel finding in the present study is that subjects with a maximum BMI SDS ≥3 at any time during the first 3 years after tumour therapy had a higher mortality rate. Analysis of obesity-related mortality in the present study showed that maximum BMI SDS was highest in those that died.

Most earlier studies on HyOb patients included those with CP. CP has the highest mortality rate in cases of tumours in the sellar region, which increases mortality risk independent of disease progression (2–4,10). A recent study reported that the standardized mortality ratio in childhood-onset CP was 17 (95% CI 6.3–37), which was higher than in both adult-onset CP and all childhood central nervous system malignancies (4). HyOb contributes greatly to increased mortality in these patients; therefore, identification of the causes of obesity-related mortality is very important (11). Sleep-disordered breathing (SDB) is common in patients with CP because of decreased melatonin production, disruption of circadian rhythm and endocrine dysfunction after treatment (12). Additionally, Manley *et al.* (11) reported that the majority of patients with CP self-reported daytime fatigue and/or sleep dysfunction, and that obstructive sleep apnoea syndrome (OSAS) or central sleep apnoea (CSA) was noted in 3 of 7 CP patients that underwent sleep evaluation. Furthermore, obesity contributes to sleep disorders. In obese children, the prevalence of OSAS and CSA is 16.7–33% and 17%, respectively (13–15). Moreover, obese patients with a high BMI have more severe SDB (11,14,15). One of the present study's subjects had severe obesity (BMI SDS 5.7) and severe CSA, which lead to death.

Patients with HyOb also have decreased sympathetic and increased parasympathetic nervous system activity (16). One study reported two patients with CP that died because of sudden cardiac problems (17). As such, cardiac arrhythmia, severe SDB and autonomous nervous system disturbance all might contribute to sudden death in children with HyOb and might increase their risk of mortality. The treatment of SDB requires a multidisciplinary approach, including a paediatric sleep physician, paediatric endocrinologist, exercise physiologist and otolaryngologist. Such patients should be evaluated for SDB via polysomnography during the early stages of HyOb and started on non-invasive ventilation as soon as possible.

Post-operative endocrinopathies are common in cases of suprasellar brain tumours and their occurrence is dependent on the extent of surgery (18,19). In the present study, 95% of the subjects had ≥1 hormone deficiency after tumour therapy; central hypothyroidism and GH deficiency were the most common pituitary hormone deficiencies in the present cohort (90% and 85%, respectively). Numerous studies reported that GH deficiency is associated with obesity in CP patients and that GH treatment reduces BMI (5,20); however, Geffner *et al.* (21) reported that GH treatment in children with CP did not ameliorate weight gain, but did have a small positive effect on BMI. In the present study, GH was the only replacement therapy that led to a reduction in BMI SDS at 6 months after

initiation and it was not associated with an increase in the risk of mortality.

In conclusion, the present findings show that a 1 SDS increase in BMI after 6 months of tumour treatment is a risk factor for mortality. Additionally, hypothalamic surgery at age <6 years and a maximum BMI SDS ≥3 are associated with increased mortality. These findings also highlight the importance of the first 6 months post-tumour therapy for preventing rapid weight gain. Observation of these risk factors could facilitate early implementation of pharmacotherapy, as well as close monitoring and treatment of ventilatory problems in patients with HyOb, which might reduce their morbidity and mortality rates.

Conflict of Interest Statement

The authors report there are no conflicts of interest – financial or otherwise – related to the work described herein and that ICMJE COI disclosure forms were submitted with the manuscript.

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