Feasibility of Fitness Testing in Children Treated for Suprapituitary Brain Tumors: A Pilot Study

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ABSTRACT

Children with suprapituitary brain tumors often become obese after surgical intervention and consecutive therapy. Although physical training was recently advocated in these patients, there is a lack of data regarding the feasibility of both exercise testing and exercise capacity of these patients. Four children surgically and pharmacologically treated for suprapituitary brain tumors were tested for body composition, muscle strength, and maximal oxygen uptake ($\dot{V}O_{2peak}$) during exercise. All patients completed the fitness testing with no adverse events. A high adiposity, lower muscle strength, and maximal exercise capacity were found in all 4 patients. $\dot{V}O_{2peak}$, $\dot{V}O_{2peak}$/kg and the VT were on average 58%, 57%, and 40% of predicted values respectively. This pilot study of 4 patients treated for a suprapituitary brain tumor found that standard fitness testing was feasible in these patients. The results indicated a marked reduction in exercise capacity and muscle strength, and increased levels of body fat in these patients. These observations suggest the need for inclusion of fitness assessments in the long-term follow-up of these children. **Key Words**: exercise capacity, brain tumors, children, muscle strength, hypothalamic obesity

INTRODUCTION

Children with a suprapituitary tumor, particularly craniopharyngioma, often become obese after tumor therapy.[1,2] This so called "hypothalamic obesity" is likely to result in poor quality of life, social isolation, reduced physical abilities, and reduced activity participation.[3] To prevent these late sequelae, which in some cases can be fatal,[4] effective strategies are needed to facilitate weight management in these patients. Improved understanding of the balance between energy expenditure (ie, physical activity) and energy intake (ie, diet) in these children should, therefore, contribute to their optimal long-term health.

Several studies have indicated that the obesity of suprapituitary tumor survivors is caused by a reduced basal metabolic rate in combination with a lack of physical activity, and not due to overeating.[5,6] Although these authors suggested physical training should be advocated in these patients, no key indicators of exercise capacity such as peak oxygen uptake ($\dot{V}O_{2peak}$) or muscle strength were determined, nor described.[5] In fact, we are aware of no studies to report the fitness levels of children surviving suprapituitary brain tumors. Because these indicators of fitness are critical to prescribe an appropriate and individualized exercise rehabilitation program for these patients, it is necessary to determine the feasibility of standard exercise testing methods in this population. Moreover, factors common to these patients (eg, visual impairment, obesity) further support and justify a study to determine the feasibility of fitness testing. With these considerations in mind, the aims of this pilot study were 2-fold: (1) to describe the feasibility of standard fitness testing in pediatric patients who developed hypothalamic obesity after being treated for a suprapituitary brain tumor and (2) to generate preliminary results on their fitness levels, compared with age- and sex-appropriate reference values.

MATERIALS & METHODS

Patients

To conduct this pilot study, we contacted all children in our hospital who were surgically treated for a brain tumor. Out of a total of 5 patients, 4 agreed to participate. The reason of decline of the fifth patient was a lack of interest in fitness and physical activity. The characteristics of the patients are shown in Table 1.

Table 1. Patients' Anthropometrical Results

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	7.7	13.9	10.3	15.6
Time since surgery (years)	2.7	4	8.9	1.5
Gender	F	F	F	M
Weight (kg)	31.3	42.3	57.8	61.2
Height (cm)	116.5	146	142	164.5
Percentile score weight for height	95	97	97	97
BMI (kg/m^2)	23.06	19.84	28.66	22.62
BMI Z-score	+3.16	+0.5	+4.45	+2.36
% Body fat	43.8	37.4	55.2	37.9
FFM (kg)	17.6	26.5	25.9	38.0

Legend: F: Female, M: Male, BMI: body mass index, FFM: Fat Free Mass.

All participating patients were treated surgically for a brain tumor (optic glioma: n = 2, germinoma: n = 1, craniopharyngioma: n = 1). Visual acuity was impaired in 3 of them, while one patient was blind. Patients were receiving desmopressine acetate for treatment of diabetes insipidus. Furthermore, they received thyroxine (thyrax; 37.5 to 50 μg), and hydrocortisone (10 mg/m^2). In addition, patient 2 and patient 3 were receiving Human Growth Hormone (2.6 IU and 3.2 IU respectively), clinical evaluation indicated that the substitutive therapy was appropriate. Informed consent was obtained from the parents after being fully informed about the test procedures and the possible risks involved. The Institutional Review Board approved all procedures. None of the children were involved in sports activities or received physical therapy aimed to increase muscle strength or endurance.

Anthropometry

Standing height and weight were measured in a standardized manner, without wearing shoes and heavy clothing, to the nearest centimeter and 100 g, respectively. The values of height, weight, and body mass index (BMI) were compared with reference values for healthy subjects matched for age and sex, and percentile scores or Z-scores were calculated.[7]

The fat free mass (FFM) of the body was estimated using a bio-electric impedance measurement with the Xitron-Hydra bio-electric measurements system (Xitron Technologies Inc. San Diego, CA). Multifrequency bioelectrical impedance analysis (BIA) measurements were performed while the child was lying quietly supine with arms and legs slightly abducted from the trunk. From the measured volumes of extracellular and intracellular water the fat free mass and the fat mass were calculated according to the manufacturer's manual.

Muscle Strength

The Hand Held Dynamometer (Citec dynamometer type CT 3001, CIT Technics, Groningen, the Netherlands) was used to measure the isometric muscle strength (in Newtons) in 4 major muscle groups (grip strength, dorsal flexors of the ankle, shoulder abductors, and quadriceps muscle strength) using standardized positions. Measurements were sequentially performed 3 times and the highest value was used for analysis. Muscle strength of the nondominant side was compared with reference values for healthy subjects matched for age and sex, and Z-scores were computed. Reference values for muscle strength were obtained from published Dutch norms.[8]

Maximal Exercise Test

Subjects performed a maximal exercise test using an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). One girl was too small to fit on our regular cycle ergometer, she was tested on a smaller mechanically braked ergometer (Tunturi, Piispanristi, Finland). The work rate started with unloaded cycling and was increased 20 Watt per minute. This protocol continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement of the investigators. During the maximal exercise test, subjects breathed through a face mask (Hans Rudolph, Inc., Kansas City, MO) connected to a calibrated expired gas analysis system (Oxycon Champion, Viasys, Bilthoven, the Netherlands). Expired gas was passed through a flow meter, an oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen uptake, carbon dioxide production, and respiratory exchange ratio (RER = $\dot{V}Co_2/\dot{V}O_2$) from conventional equations.

Ventilatory threshold (VT) was used as an effort-independent measure of fitness, and was determined using the criteria of an increase in both the ventilatory equivalent of oxygen ($\dot{V}E/\dot{V}O_2$) and end-tidal pressure of oxygen ($PETO_2$) with no increase in the ventilatory equivalent of carbon dioxide ($\dot{V}E/\dot{V}CO_2$).[9] Heart rate (HR) was measured continuously during the exercise test by a bipolar ECG (Hewlett-Packard, Amstelveen, the Netherlands); transcutaneous oxygen saturation (SaO_2%) was monitored at the index finger by pulse oxymetry (Nellcor 200 E, Breda, The Netherlands). Absolute $\dot{V}O_{2peak}$ was taken as the average O_2 uptake over the last 30 seconds during the maximal exercise test and represents the gold standard approach to assessing aerobic fitness in humans. Peak oxygen uptake was normalized to total body mass and fat free mass (FFM) to account for differences in body size and body composition. A maximal effort was defined as achieving an RER greater than or equal to 1.0, or reaching a HR_{peak} greater than 180.[10] Reference values were obtained from a population of 175 healthy Dutch children and adolescents.[11]

RESULTS

All fitness tests were tolerated well and completed uneventfully. The results of the fitness tests can be appreciated from Table 2.

Table 2. Muscle Strength and Exercise Capacity Data of the 4 Patients

	Patient 1	Patient 2	Patient 3	Patient 4
Grip strength (Z-score)	-2.1	-5.0	-3.2	-6.2
Ankle dorsal flexors (Z-score)	-0.9	-1.5	-0.7	1.1
Knee extensors (Z-score)	-2.6	0.1	-1.5	-1.3
Shoulder abductors (Z-score)	1.3	0.3	-0.5	-0.2
Global muscle strength score (Z-score)	-1.1	-1.5	-0.9	-1.8
HR_{peak} (beats per minute)	175	192	194	186
RER_{peak} (= $\dot{V}CO_2/\dot{V}O_2$)	1.05	1.15	1.1	1.07
$\dot{V}O_{2peak}$ (mL/min) [% pred]	909 [63]	1440 [58]	991 [59]	1443 [47]
$\dot{V}O_{2peak}$/Kg (mL/kg×/min^{-1}) [% pred]	29.0 [71]	34.0 [77]	17.1 [42]	23.6 [43]
$\dot{V}O_{2peak}$/Kg (mL/kg FFM×min^{-1})	51.6	54.3	38.3	38.0
VT (mL/min) [% pred]	15.5 [43]	19.2 [53]	10.1 [29]	14.2 [33]
VT (% $\dot{V}O_{2peak\ predicted}$) [% pred]	38 [43]	44 [53]	25 [29]	26 [33]

Legend: HR_{peak}: peak heart rate, RER_{peak}: peak Respiratory Exchange Ratio, $\dot{V}O_{2peak}$: peak oxygen uptake, $\dot{V}O_{2peak}$/Kg: peak oxygen uptake per kg body mass, VT: ventilatory threshold, FFM: Fat Free Mass.

All patients had a high percentile score for weight for length; 3 patients had a body mass index (BMI) Z-score above + 2 SDs, indicating overweight. The percent body fat values ranging from

37% to 55% would be considered moderate to marked obesity.[12]

During the maximal exercise test, peak HR averaged 187 beats per min (range 175 to 194) and the average RER_{peak} was 1.09 (range 1.05 to 1.15). These results are important because they indicate that the patients gave sufficient effort and exercised to a maximal or very close to a maximal level. None of the patients desaturated during exercise. Either expressed in absolute terms or relative to body mass, the $\dot{V}O_{2peak}$ of each patient was significantly reduced, with a wide variation in predicted $\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$/kg. The VT – a submaximal indicator of fitness – could be determined in all subjects and was also reduced in each patient representing, on average, 40% of $\dot{V}O_{2peak}$.

Muscle strength tests were also performed without difficulty. Grip strength and muscle strength of the knee extensors showed the lowest values. Global muscle strength score, representing the average values from the four muscle groups, was reduced by -1 SD to -2 SD compared to age and gender matched reference values.

DISCUSSION

The purpose of this pilot study was to describe the feasibility of exercise testing for patients undergoing surgical treatment for a suprapituitary brain tumor and to compare the initial findings with predicted values from healthy children. These 4 patients illustrate that children after their surgical treatment for a suprapituitary brain tumor can have a significantly reduced muscle strength and exercise capacity compared to healthy peers. The exercise capacity is significantly lower compared to other pediatric malignancies such as acute lymphoblastic leukemia,[13] and compared to other children who survived treatment for various solid (nonbrain) tumors.[14]

In our patients, the $\dot{V}O_{2peak}$ in absolute terms ranged from 63% to 47% of predicted. In addition, their $\dot{V}O_{2peak}$/kg and the VT were severely reduced as well. Even when corrected for fat free mass, the $\dot{V}O_{2peak}$/FFM was significantly lower compared to values reported in the literature for obese and healthy children (current study: 46 [range 38-54.3] mL/kg FFM×min^{-1}, 59 and 58 mL/kg FFM×min^{-1} in obese and healthy children respectively).[15] It is important to note that this impaired exercise tolerance can not be ascribed to lack of effort or extreme fatigue levels since each patient experienced high values of RER and HR at peak exercise indicating an effort comparable to most healthy children.[12]

While this pilot study recruited a small number of patients, we did include all but one patient from our tertiary center. With this sample of children, we confirmed the feasibility of fitness testing in these patients and generated unique data on the relatively impaired exercise capacity of suprapituitary brain tumor survivors, compared with healthy children. To our knowledge, this is the first study of its kind and supports the need for a larger multicentre study to reveal the patho-physiological factors leading to the reduction in exercise capacity and muscle strength. We chose to evaluate maximal exercise capacity on a bicycle ergometer as a safety feature for our patients to support their body weight during exercise and for reasons of impaired visual acuity.[16] We recommend using this type of ergometry when testing this population. Our results suggest that these children experience a low level of exercise tolerance that is likely to predispose them to further physical inactivity.

Patients with craniopharyngioma and other brain tumors are at risk for developing 'hypothalamic obesity.'[1,17] The major risk factor for becoming obese is hypothalamic damage due to tumor, surgery, or radiation.[17] However, reduced physical activity levels or an increased appetite are also observed in these patients, also leading to an increased body mass.[5,18] The physical inactivity and increased appetite might be caused by changed hormonal levels in these patients, especially high leptin and insulin levels.[17,19] Cranial radiation has been identified as a risk factor for a reduced exercise capacity in other pediatric malignancies,[13,20] probably due to a depressed mitochondrial function, although physical inactivity alone could propagate the reduced exercise tolerance, and this could also play a role in our patient group. Consequently, these children are excellent candidates for exercise programs designed to increase fitness.

Recently it has been shown that low fitness levels are related to cardiovascular disease in young adults.[21] Based on our results, the children in the current study may be at high risk for developing cardiovascular disease.[22] Prescribed exercise programs might not only increase exercise capacity, but reduce obesity and reduce the risk for co-morbidity as well.[23] The effects of an exercise therapy intervention in children with brain tumors has not been described in the literature, however, exercise might have positive effects on exercise capacity, might reduce body fat levels, and increase quality of life as it does in children with leukemia.[24] The reduced visual capacity and the observed obesity in these patients provide a challenge to a specific patient-tailored design of this program. Many activities are difficult to perform for children with limited visual capacity, which in turn also contributes to a reduced exercise capacity and obesity.[5,25]

However, an exercise program involving aerobic exercises, such as swimming, walking on a treadmill, cycling on a stationary or tandem bike, and ball-games for improving fitness may be useful for this patient population. In light of deficits in muscle strength, a combination of short-term high intense exercises, such as jumping, sprinting, as well as resistance training[24,26] may also be considered for improving muscle strength.

CONCLUSION

This pilot study of 4 patients treated for a suprapituitary brain tumor found that standard fitness testing was feasible in these patients. The results indicate a marked reduction in exercise capacity and muscle strength, and increased levels of body fat in these patients. These observations suggest that the long-term follow-up of these children should include fitness assessments, which can be used to prescribe an appropriate and individualized exercise rehabilitation program.

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