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CASE REPORT

Evaluations of Exercise Intolerance With Cardiopulmonary Exercise Tests in a 24-year-old Young Male With Obesity With Tetrahydrobiopterin Deficiency: A Case Report

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Abstract

Phenylketonuria (PKU) is a rare amino acid metabolism genetic disorder. Tetrahydrobiopterin (BH4) metabolism defects cause variant PKU. BH4 coenzyme deficiency disables phenylalanine metabolism into tyrosine, causing brain damage and intellectual impairment. Patients follow a low-phenylalanine diet for life, increasing the risk of obesity, hypertension, and metabolic syndrome. A 24-year-old male patient with BH4 deficiency underwent a pulmonary function test and cardiopulmonary exercise test (CPET). Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were within normal values, with an 80.68 % ratio. The 20-W bicycle exercise test indicated moderate functional impairment (27.3 ml/kg/min of peak oxygen intake). The test achieved 81 % and 70 % of the target and reserve heart rates, respectively. The patient’s body mass index was 29.9 kg/m², causing a high resting metabolic rate and oxygen uptake. The need for oxygen uptake is more prominent during high-intensity exercise, thus his functional impairment was caused by obesity. CPET evaluates cardiorespiratory fitness in patients with PKU, providing appropriate aerobic and resistance training to improve prognosis with a weight control program.

Keywords: Cardiopulmonary exercise test, Exercise intolerance, Obesity, Phenylketonuria, Tetrahydrobiopterin deficiency

1. Introduction

Phenylketonuria (PKU) is a rare autosomal recessive disorder of abnormal amino acid metabolism, with varying prevalence in different countries,1 with approximately 1 in 58,000 incidences in Taiwan.2 Among them, approximately 70%—80% are typical PKU (also known as PAH deficiency), and approximately 20%—30% are tetrahydropterin deficiency (BH₄ deficiency). The most common type of BH₄ deficiency is the 6-pyruvoyl-tetrahydropterin synthase (P'TPS) deficiency.3 Phenylalanine is an essential amino acid for the human body. BH₄ coenzyme deficiency disables phenylalanine metabolism into tyrosine, and toxic metabolite accumulation in the body, resulting in brain damage and severe intellectual impairment.1–4 Treatment for patients with...
BH₄ deficiency requires supplementation with sapropterin, levodopa (L-Dopa), 5-hydroxytryptophan (5-HTP) and other substances. Patients with PKU require a low-phenylalanine diet for life, thus patients tend to eat carbohydrate-rich foods, and some studies emphasized a higher prevalence of obesity in patients with PKU. However, the research data and interpretation of cardiopulmonary exercise test (CPET) in the PKU population remain lacking, thus this article attempts to present the CPET results of patients with PKU to provide more information on diagnosis, treatment, prognosis, and exercise prescription.

2. Case report

A 24-year-old male patient with BH₄ deficiency since childhood with a PTPS gene mutation (exon 5 c.259C > T, p.P87S/c.155A > G, p.N52S) was stable in pediatric outpatient follow-up for >20 years while taking sapropterin, L-Dopa, and 5-HTP regularly. He was referred to the rehabilitation clinic for a pulmonary function test (PFT) and CPET due to obesity and exercise intolerance. Physical assessment revealed a height of 186.8 cm and a weight of 104.4 kg. The patient underwent PFT and CPET with informed consent and without any contraindications, following the recommendations of the American College of Sports Medicine’s Guidelines for Exercise Testing and Prescriptions (ACSM guidelines), 10th edition.

PFTs were performed by spirometry, collecting forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and maximal voluntary ventilation. The CPET equipment consists of a flywheel, a flow module, a gas analyzer and an electrocardiogram (ECG) monitor. A detailed demonstration was given before the test, and the patient was in normal health and was able to understand and follow the doctor’s instructions. Then, we performed symptom-limited exercise tests using a 20-W-per-minute bicycle protocol. Heart rate (HR), blood pressure (BP), minute ventilation (VE), oxygen uptake (VO₂), carbon dioxide output (VCO₂), respiratory exchange ratio (RER) and partial pressure of end-tidal carbon dioxide (PETCO₂) were collected. The predicted maximum HR (HRmax) was 196 beats/min, which was derived from the prediction formula 216.6 – (0.84 × age). VO₂ (ml/kg/min) was recorded sequentially during the test and divided by 3.5 to present exercise capacity as the metabolic equivalent of tasks (MET). The predicted maximum VO₂ (VO₂ max pred) was determined by age, sex, and body weight. HR recovery (HRR) is the difference between the HR 1 min after the test and the peak HR. The anaerobic threshold (AT) was determined by the VE/VO₂ and VE/VCO₂ methods.

The VO₂ max was determined if any of the following criteria were met: 1) VO₂ was maintained at a plateau with the increase of power; 2) HR failed to increase with the increase of power; 3) peak RER of ≥1.10. The test was terminated following the patient’s request due to severe fatigue and leg soreness. The maximum effort was considered to have been reached when the peak RER exceeds 1.10. Angina, cyanosis, or dizziness were not observed during the examination, with no ST elevation or displacement on the ECG monitor. HR and BP rose steadily as the workload increased. Benchmark values and test results are presented in Tables 1 and 2.

The peak HR was 81.6 % of the predicted value of HRmax with the patient’s best efforts, suggesting a lesser risk of chronotropic insufficiency in the patient. The 20-W cycling exercise test revealed an HRR of 28 and a maximum exercise capacity of 7.8 METs (maximum oxygen uptake: 27.3 ml/
kg/min), which is 64.83 % of the predicted value, indicating moderate functional impairment. The 6-min walk test was 621 m. FVC and FEV1 were within the normal range, with FEV1/FVC of 80.68 %, and breathing reserve was 8.26 %. Lung function demonstrated no obvious abnormalities, with no signs of lung disease.11 The slope of VE/VCO2 was 28.8, indicating sufficient ventilation efficiency. No myocardial ischemia or arrhythmia were found during exercise, and the maximum oxygen consumption standard defined by ACSM guidelines was reached. The resting HR was 75 beats/min, and the maximum HR during exercise was 160 beats/min. The test reached 81 % of the target HR and 70 % of the reserve HR, indicating no obvious abnormality in the heart performance. However, the patient has obesity, with a body fat rate of 28 %, a body mass index of 29.9, a high resting metabolic rate and resting oxygen uptake. The need for oxygen uptake was more prominent during high-intensity exercise. Therefore, we concluded that his lower maximum predicted oxygen uptake and functional impairment were caused by obesity.

3. Discussion

Herein, we analyzed the exercise capacity of a 24-year-old male patient with PKU, conducted an objective assessment through CPET and further analyzed the test results to determine the main reasons for limiting exercise performance. Detailed exercise prescriptions are provided to improve prognosis. The exercise performance in our case was similar to that of patients with obesity. People with PKU spend less time exercising in moderate intensity exercise, consume less energy, and energy intake from carbohydrates is higher, which may be related to the underlying mechanism of obesity in patients with PKU.12

The analysis of CPET in patients with PKU was lacking before this study, and without a comprehensive interpretation of CPET results and without providing a correct differential diagnosis. Fick's equation states that oxygen uptake is the product of cardiac output and arteriovenous difference, reflecting central, and peripheral oxygen supply, respectively.13 Poor exercise capacity may be caused by pulmonary, cardiovascular, and metabolic disorders or physical discomfort. Lower peak oxygen uptake and anaerobic thresholds were observed in patients with obesity,14 which is similar to our case. Patients with obesity may have good cardiovascular fitness but poor work capacity because of higher metabolic demands during moderate to high-intensity exercise. Additionally, they are prone to hypoxemia at rest due to atelectasis of peripheral lung units. However, this situation improves during exercise, because tidal volume reopens collapsed lung units, thereby improving arterial oxygenation, which is the only lung condition that can be improved by exercise.15 Additionally, respiratory compensation from lactic acidosis may be less than normal at peak oxygen uptake because of increased work of breathing and decreased maximal inspiratory and expiratory pressure in patients with obesity.16

To our knowledge, this is the first study to assess physical fitness in patients with PKU through CPET. The test results revealed a moderate degree of the functional defect (64.38 % of predicted VO2 max), mainly affected by body obesity, with no significant cardiovascular or pulmonary limitations.
CPET is a valuable diagnostic tool that can be used to assess the cardiorespiratory fitness of patients with PKU, and the results can be used to provide exercise prescriptions for patients to perform aerobic and resistance exercises under safe conditions with a suitable weight control program for a better prognosis.

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