



Laryngeal Spasm Mimicking Asthma and Vitamin D Deficiency

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We present a woman with heterozygous carnitine palmitoyl transferase 2 (CPT-2) deficiency who in the last 6 months suffered from episodic dyspnea and choking. Symptoms could not be attributed to her muscular energy defect, since heterozygous CPT-2 deficiency is usually asymptomatic or causes only mild muscle fatigability. Myopathy is usually triggered by concurrent factors, either genetic (additional muscle enzymes defects) or acquired (metabolic stress). The patient was referred to our respiratory clinic for suspect bronchial asthma. Spirometry showed mild decrease in inspiratory flows. Methacholine challenge was negative. Dyspnea was triggered by hyperventilation-induced hypocapnia, which produced marked decrease in airflow rates, particularly in inspiratory flows, consistent with laryngospasm. Nutritional assessment of the patient showed low serum level of calcium and vitamin D, attributable to avoidance of milk and dairy products for lactose intolerance and to insufficient sunlight exposure. After calcium and vitamin D supplementation episodic laryngospasm disappeared and hypocapnic hyperventilation test induced very mild change in airflow rates. Calcium and vitamin D deficiency may favour laryngeal spasm mimicking asthma, particularly in subjects with underlying myopathy.

Key Words: Laryngeal spasm; asthma; vitamin D deficiency; calcium deficiency

INTRODUCTION

Asthma-like symptoms are anxiety producing for patients, and improper diagnosis leads to inappropriate use of asthma medications, unnecessary office and emergency room visits and referral to specialists to determine the cause. Vocal cord dysfunction (VCD) is responsible for 15% of referrals for dyspnea on exertion and frequently leads to multiple emergency room visits.

CASE REPORT

A 47-years-old white woman, heterozygous for CPT-2 deficiency presented with 6 months history of severe episodic dyspnea and choking, triggered by emotions and exercise, and worsening dysphonia.

The patient was simple heterozygote for S113L CPT2 mutation (ratio CPT/citrate synthase = 1.88), inherited from her father. Her unique son, 25-years-old, had the same genetic abnormality.

She had a lifelong history of muscular symptoms, including myalgia, cramps and contractures, fatigability and constipation, which worsened recently. She reported a single episode of myoglobinuria, triggered by high fever. One year before the current presentation, she underwent total thyroidectomy. A few months later she developed rectal sphincter spasm requiring surgery, and, subsequently, chronic atonic stipsis, diagnosed by defecography.

Lower limbs electromyography was normal.

In view of her dysphonia, videolaryngostroboscopy and fiberoptic laryngoscopy had been performed, which showed only vocal cords hyposthenia with compensatory false cords hypertrophy. After unsuccessful attempt of logopedic therapy the patient was sent to our respiratory clinic suspecting that episodic dyspnea was due to bronchial asthma, despite negative personal and family history.

Physical examination disclosed a thin and anxious woman with easy fatigability, worried about dyspnea, disabling breathy hypophonia and choking episodes. At spirometry, lung volumes and expiratory flows were normal, while inspiratory flow-volume curve was consistent with variable extrathoracic airway obstruction. Methacholine inhalation challenge was negative, as well as skin prick tests for common inhalant allergens. The hyperventilation test,¹ performed in hypocapnic condition (that is with an end-tidal partial pressure of CO₂ below 35 mmHg), triggered stridor and choking, associated with a dramatic decrease

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Received: January 7, 2013; Accepted: January 29, 2013

• There are no financial or other issues that might lead to conflict of interest.

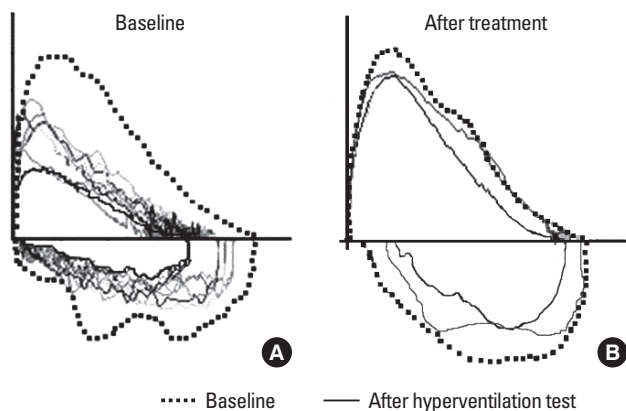


Figure. Flow-volume loop before and after the hyperventilation test. (A) During calcium and vitamin D deficiency. (B) After treatment with calcium and vitamin D for 2 months.

in FEV1 and in both expiratory and inspiratory airflow rates, within the first minute (Figure A), which lasted more than 5 minutes. Laboratory investigations showed low values of serum calcium (2.1 mmol/L, normal range 2.2-2.6 mmol/L) and 25-hydroxyvitamin D (18.7 nmol/L, normal range 30-93.8 nmol/L), which were due to the fact that the patient avoided milk and dairy products for lactose intolerance, and rarely exposed to sunlight. There was no compensatory hyperparathyroidism (PTH 39 pg/mL, normal range 10-65), probably due to the previous thyroid surgery.

After nutritional supplementation for 2 months (calcium and cholecalciferol 5,000 U/weekly), serum calcium increased to 2.33 mmol/L, and 25-hydroxyvitamin D to 147.3 nmol/L. The patient reported improved dysphonia and no other choking attacks. The hypocapnic hyperventilation test showed only mild change in airflow rates (Figure B).

DISCUSSION

We describe a woman with heterozygous CPT-2 deficiency, in whom the recent development of episodic dyspnea and choking had been wrongly attributed, at first, to her myopathy, and, subsequently, to bronchial asthma. CPT-2 is an ubiquitous enzyme in humans, designed for the transport of long chains fatty acids from cytosol into the mitochondrial matrix of mammalian cells via β -oxidation.² The clinical presentations of CPT-2 deficiency are manifolds, according to the age of onset and the tissue distribution of the symptoms. Muscular involvement is the most common manifestation³ with recurrent attacks of myalgias and muscle stiffness or weakness, occasionally associated with myoglobinuria. In heterozygous subjects, as the case under discussion, clinical symptoms are mild, consisting only in slight muscle fatigability, but may be worsened by other coexisting factors, either genetic (concurrent partial deficiency in other muscle enzymes) or acquired.⁴ Thus, it seemed unlikely that

congenital myopathy was the cause of dyspnea in our patient, and the same applies for asthma, in view of the negative history and negative methacholine challenge.

Vocal cord dysfunction (VCD), that is a paradoxical adduction of the vocal cords, seems an attractive explanation in our patient, as it may mimic bronchial asthma and is often triggered by emotions and exercise.⁵ However, VCD often improves with vocal therapy, while it was ineffective in our case. We may suppose that in our patient VCD was a manifestation of laryngeal tetany due to calcium and vitamin D deficiency, as it improved only after correction of the defect. We previously observed that in subjects with calcium deficiency, hyperventilation in hypocapnic conditions induces prolonged laryngeal spasm.¹ Laryngeal spasm from hypocalcemia is a well-recognized feature in children⁶ but it has also been reported in the elderly.⁷ Hypocalcemia leads to increased neuromuscular irritability, causing paresthesias and muscular cramps and, when severe, laryngospasm, generalized tonic muscle cramps and seizures. Hypocalcemia is worsened by the excessive hyperventilation which occurs during anxiety, fear, and stress situations, as respiratory alkalosis causes calcium ions binding to proteins.⁸ Decreased intracellular calcium inhibits the actin-myosin sliding, favouring the persistence of contracture.

In our patient, CPT-2 deficiency further contributed to contracture, through lowered mitochondrial-oxidation, with consequent decreased ATP availability.

Vitamin D deficiency and hypocalcaemia are quite common particularly in areas where there is little ambient sunlight, as in our latitude. It has been reported that as many as 25% of elderly patients, who spend most their life indoor, suffer from this disorder.

This case suggests that episodic laryngeal spasm may be sustained by calcium and vitamin D deficiency and may be externalized by stressful situations causing hyperventilation. The reaction is favoured by underlying myopathy.

ACKNOWLEDGMENTS

This study was supported by Italian Ministry of University and Research (2007HPRM9S).

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