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ORIGINAL ARTICLE

Exercise-induced nausea and vomiting: another sign and symptom of pheochromocytoma and paraganglioma

Kathryn S. King · Nissar A. Darmani · Marybeth S. Hughes · Karen T. Adams · Karel Pacak

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Abstract A cohort of nine patients, mostly young adults, presented with a new sign/symptom of pheochromocytoma/paraganglioma: exercise-induced nausea and vomiting. The aims of this article are to introduce this sign/symptom and offer a possible hypothesis for the observation. Following a 2000 report from a paraganglioma patient experiencing exercise-induced nausea and vomiting, we began asking patients about instances of nausea and vomiting with exercise. A total of nine patients, 4.4% of our pheochromocytoma/paraganglioma population, presented with reports of exercise-induced nausea and vomiting, initially with moderate-to-intense levels of exercise, at the first presentation of their disease. All of these patients reported a cessation of exercise–induced nausea and vomiting following the removal of their primary tumor. Two patients with metastatic disease to the lungs reported a recurrence of exercise-induced nausea and vomiting. The majority of patients studied were young adults with mean onset age of 19.4 years (range of 9–51 years) and the mean age of diagnosis being 24.1 years (range of 11–53 years). Exercise-induced nausea and vomiting should be considered a sign/symptom of pheochromocytoma/paraganglioma and should be addressed in the clinical evaluation of these patients, especially in young adults. Whether exercise-induced elevated catecholamine levels could account for the induced nausea and vomiting via activation of adrenergic receptors in the area postrema remains to be established.

Keywords Nausea · Vomiting · Pheochromocytoma · Paraganglioma · Norepinephrine · Epinephrine · Catecholamine

K. S. King · K. T. Adams · K. Pacak (✉)
Section on Medical Neuroendocrinology, Reproductive and Adult Endocrinology Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development NICHD, National Institutes of Health NIH, Building 10, CRC, 1-East, Room 1-3140, 10 Center Drive, MSC-1109, Bethesda, MD 20892-1109, USA
e-mail: karel@mail.nih.gov

N. A. Darmani
Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA 91766, USA

M. S. Hughes
Surgical Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

Introduction

Pheochromocytomas and paragangliomas (chromaffin cell tumors of the sympathetic or parasympathetic ganglia) are diagnosed either biochemically based on the measurements of catecholamines and their metabolites in the blood and/or urine, or by specific imaging modalities [1–3]. The clinical manifestation of pheochromocytomas/paragangliomas secreting excess catecholamines is typically characterized by symptoms of elevated blood pressure, heart palpitations, increased perspiration, and anxiety [4–6]. Less commonly, pheochromocytoma/paraganglioma patients can present with signs and symptoms such as pallor, headaches, flushing, nausea, and vomiting, which often occur during hypertensive spells [5]. These events usually subside following the decrease in their plasma catecholamine levels.

In 2000 a 23-year-old man presented to the National Institutes of Health (NIH) for suspected pheochromocytoma/paraganglioma. The patient's history showed that he began experiencing episodes of nausea during intense

exercise at age 20 (exercise level determined based on guidelines by the CDC and ACSM) especially when jogging and lifting weights, which would cause him to discontinue exercise after which he would vomit. These events became worse over the years to the point where he would vomit every time he exercised (even when exercise was considered light, such as brisk walking). Following the removal of the patient's primary abdominal tumor, exercise-induced nausea and vomiting ceased, and the patient has been free of these signs/symptoms since.

Subsequent to this report, we began asking patients about experiences with nausea during exercise, and nausea and vomiting after exercise. Throughout the clinical interview, physicians especially focused on a number of important questions surrounding patient's experiences with exercise-induced nausea and vomiting. During this investigation, a total of 206 patients with pheochromocytoma/paraganglioma were studied at the NIH, and we have identified a cohort of nine patients who initially presented with exercise-induced nausea and vomiting.

Subjects and methods

A total of 206 patients with diagnosed pheochromocytoma/paraganglioma have been studied at the NIH and nine of them initially presented with exercise-induced nausea and vomiting in addition to the classical symptoms of pheochromocytoma/paraganglioma on the first presentation of their disease.

On initial clinical evaluation all pheochromocytoma/paraganglioma, patients were asked about their signs and symptoms related to catecholamine excess including whether or not they experienced exercise-induced nausea and vomiting. If the patient had experienced exercise-induced nausea and vomiting, they were asked specific questions including: (a) whether nausea and vomiting was only present during exercise or when they were sedentary; (b) what intensity of exercise initially induced nausea and vomiting; (c) whether the intensity of exercise or duration of exercise affected the severity of nausea and vomiting; (d) how long after exercise initiation did nausea and vomiting occur; (e) whether other signs/symptoms of pheochromocytoma/paraganglioma were involved; (f) whether their experiences of nausea and vomiting changed over time (e.g., did the patient begin experiencing nausea and vomiting after less intense exercise); and (g) whether exercise-induced nausea and vomiting subsided after removal of the primary tumor. Thus, from the cohort of 206 pheochromocytoma/paraganglioma patients, we identified nine individuals who complained of exercise-induced nausea and vomiting on the first presentation of their disease.

Characteristics of these patients, outlined in Table 1, show the mean age of symptom onset as 19.4 years (range: 9–51 years) and the average age of diagnosis as 24.1 years (range: 11–53 years). Biochemical data at first presentation to the NIH, but not necessarily the first presentation of disease, (patients gave informed consent prior to any testing at the National Institutes of Health) for the nine patients showed noradrenergic phenotypes (Table 2).

Occurrence of exercise-induced nausea and vomiting at the initial presentation of disease appeared at varied exercise levels ranging from light to intense, as defined by the CDC and ACSM guidelines [7]: with one patient stating initial presentation of the sign/symptom with light exercise, three patients with moderate exercise, two patients with moderate-to-intense exercise, and three patients with intense exercise (Table 3). During and following physical

Table 1 Patient characteristics associated with exercise-induced nausea and vomiting

Pt	Age of symptom onset	Age of diagnosis	Age of metastasis	Gender	Genetic mutation	Biochemical phenotype
1	9	11	13	M	SDHB	NE + NMN + MN
2	9	12	19	M	SDHB	NE
3	10	18	31	F	SDHB	NE + EPI + NMN
4	13	23	23	F	SDHB	NE + NMN
5	14	14	17	M	SDHB	NE + NMN
6	20	23	23	M	SDHB	NE + NMN
7	22	33	36	F	SDHB	NE + NMN
8	27	30	No meta diagnosis	F	No known mutation	NE + EPI + NMN + MN
9[a]	51	53	No meta diagnosis	F	No known mutation	EPI + NMN + MN

Biochemical phenotype data come from the first plasma catecholamine and metanephrine test preformed on each patient at the National Institutes of Health (NIH), not necessarily at the first presentation of their disease

Age of symptom onset age of onset of initial exercise-induced nausea and vomiting associated with pheochromocytoma/paraganglioma, *Age of diagnosis* age of diagnosis of pheochromocytoma/paraganglioma, *Age of metastasis* age of diagnosis of metastatic pheochromocytoma/paraganglioma, *EPI* epinephrine, *F* female, *M* male, *Meta* metastatic, *MN* metanephrine, *NE* norepinephrine, *NMN* normetanephrine, *Pt* patient

[a] Biochemistry tests in patient 9 prior to testing at the NIH demonstrated elevated norepinephrine levels

Table 2 Biochemical phenotype at first visit to NIH

Pt	NE	EPI	DA	NMN	MN	Disease state at time of blood draw
1	**3071**	16	11	**1609**	**275**	Mets in bone and lungs
2	**503**	17	12	109	39	Mets in bone
3	**7679**	**231**	28	**18976**	56	Mets in bone
4	**598**	4	7	**187**	48	Mets in bone
5	**504**	7	?	**135**	7	Mets in bone
6	**15212**	29	**696**	**5700**	21	Mets in bone primary abdominal
7	**789**	7	<38	**285**	24	Mets in lung
8	**2161**	**363**	23	**2507**	**614**	Primary adrenal
9[a]	389	**626**	17	**170**	**922**	Primary adrenal
Normal ranges	80–498 (pg/mL)	4–83 (pg/mL)	3–46 (pg/mL)	18–112 (pg/mL)	12–61 (pg/mL)	

The biochemical testing reported is from the first biochemical test preformed on the patients at the National Institutes of Health (NIH), not necessarily at the first presentation of disease. Six patients presented to the NIH with solely metastatic disease (pts 1, 2, 3, 4, 5, 7)

? = Some of the patients did not have dopamine or chromogranin A measured

Bold numbers indicate biochemical levels above the upper reference limit

CgA chromogranin A, *DA* dopamine, *Disease state* disease state at time of biochemical testing, *EPI* epinephrine, *MN* metanephrine, *Mets* metastatic lesions, *NE* norepinephrine, *NMN* normetanephrine, *Pt* patient, *Primary* original pheochromocytoma/paraganglioma

[a] The patient showed elevated norepinephrine levels immediately prior to admission to the NIH

Table 3 Exercise characteristics associated with initial report of nausea and vomiting

Pt	Exercise-inducing nausea and vomiting	Exercise intensity level	Course of nausea and vomiting	Additional symptoms
1	Biking	Moderate	Ceased after removal of primary tumor but recurred with metastatic lesions	HTN, HA
2	Running	Moderate	Occurred until removal of primary abdominal tumor	Sweating, tachycardia
3	Running	Moderate	Occurred until removal of primary adrenal tumor	HA, leg weakness, tachycardia
4	Running	Intense	Occurred until removal of primary abdominal tumor	HTN, HA, tachycardia, tumor-related pain
5	Biking	Moderate-to-intense	Occurred until removal of primary adrenal tumor	HTN, tachycardia
6	Jogging	Intense	Occurred until removal of primary abdominal tumor	Tachycardia
7	Swimming	Intense	Ceased after removal of primary tumor but recurred with metastatic lesions	HA, palpitations, sweating
8	Playing with son	Light	Patient has had primary tumor removed but has not yet been cleared to exercise	HA, palpitations, sweating
9	Biking	Moderate-to-intense	Occurred until removal of primary adrenal tumor	HA, sweating

Exercise intensity level was determined based on guidelines by the CDC and ACSM. All patients reported the continuation of both nausea during exercise and vomiting following exercise until the removal of the primary tumor. Some patients with metastatic disease continued to have symptoms of nausea and vomiting on exercise

HA headache, *HTN* hypertension, *Pt* patient

activity, these patients experienced the classical pheochromocytoma/paraganglioma symptoms of elevated blood pressure, heart palpitations, profuse sweating, in some cases headaches, and all concomitantly experienced nausea during exercise followed by vomiting at the cessation of exercise. The patients studied were all adequately conditioned, with the adults reporting having been exercising regularly until the signs/symptoms started, and the parents of the children stating that their offspring had been very active prior to the reported signs/symptoms. The majority of patients stated that the sign/symptom of exercise-induced nausea and vomiting grew worse with time and that the sign/symptom could eventually be elicited during instances of light exercise (such as carrying a suitcase or picking up a child). Some learned to control the symptoms by backing off the exercise when starting to become

nauseous in an attempt to avoid vomiting. Patients reported that on removal of the primary tumor, exercise-induced nausea and vomiting ceased (Table 3).

For ethical reasons, patients were never subjected to exercise tests to try and mimic the symptoms, nor were they encouraged to continue exercising following reports of these symptoms until the offending pheochromocytoma/paraganglioma could be removed.

Six of the nine patients presented to our institution with metastatic disease, and one patient (patient 6) presented with metastatic lesions in the bones as well as a primary abdominal tumor, and all described experiencing exercise-induced nausea and vomiting on the first presentation of their disease (not necessarily at the presentation of metastatic disease). Patients with metastatic lesions in the organs such as the lungs (patients 1 and 7) reported a recurrence of exercise-induced nausea and vomiting following the development of metastatic tumors. Those patients with metastatic lesions solely in the bones, however, did not report a recurrence of exercise-induced nausea and vomiting.

Interestingly, seven of the nine patients had SDHB gene mutations. Whether exercise-induced nausea and vomiting is more common in patients with SDHB mutations over other genetic mutations remains to be established.

Discussion

The early age of onset, noradrenergic biochemical phenotype, genetic mutation, and extraadrenal location of the primary tumor among these patients suggest that exercise-induced nausea and vomiting may be an important sign/symptom in some pheochromocytoma/paraganglioma patients.

Published research in dogs indicate that activation of α_2- and possibly α_1-adrenergic receptors in the area postrema, a chemoreceptor trigger zone located on the floor of the fourth ventricle in the brain stem, by catecholamines such as norepinephrine could be responsible for the induced nausea and vomiting exhibited in these patients [8]. The area postrema is a circumventricular organ that lacks blood brain barrier and thus could be accessible to compounds circulating in the blood [9], including catecholamines in pheochromocytoma/paraganglioma patients. Indeed, systemic or intramuscular administration of epinephrine or selective α_2- or α_1-adrenoceptor agonists induce vomiting in dogs in a dose-dependent manner which can be selectively blocked by their corresponding antagonists [8]. Moreover, direct injection of norepinephrine and epinephrine into the third or the lateral ventricle have been shown to induce emesis, probably through activation of α_1- and α_2-adrenergic receptors in the chemoreceptor zone of the fourth ventricle [10]. Our results indicate that exercise increases the amount of circulating catecholamines in pheochromocytoma/paraganglioma patients, this could potentially lead to activation of adrenergic α_1- and α_2- receptors in the area postrema and therefore, would induce nausea and vomiting.

In clinical practice, low doses of clonidine are commonly used as an α_2-adrenergic receptor agonist to support the biochemical diagnosis of pheochromocytoma/paraganglioma, which, at least theoretically, should also induce nausea and vomiting via the central nervous system [11, 12]. However, in our experience with clonidine testing, we have never had a patient complain of nausea or vomiting during or following the test. Recent studies also seem to support clonidine as a nausea suppressor as opposed to a nausea inducer [13–15]. This is based on the hypothesis that clonidine acts as a sedative as well as suppressing noradrenergic activity via activation of presynaptic α_2-receptors [15]. Thus, combination of these two effects is thought to lead to its antiemetic nature [15]. On the other hand, activation of postsynaptic α_2-adrenoceptors by large doses of catecholamines present in pheochromocytoma/paraganglioma patients could lead to emesis.

Exercise is known to produce a variety of gastrointestinal disturbances including nausea, diarrhea, and abdominal cramps [16]. During exercise, blood flow is mainly directed toward working muscles, skin (for thermoregulation), the heart, and the brain at the expense of less-demanding organs such as the visceral organs. The gastrointestinal symptoms associated with exercise could be a consequence of vasoconstriction of splanchic and mesenteric vascular beds as a result of increased activation of α_1-adrenergic receptors due to increased release of norepinephrine from sympathetic nerves. The decrease in blood flow in the visceral organs may reduce the "wash effect" of cardiovascular system and the released emetogens (norepinehrine, serotonin, prostaglandins, or leukotrienes) during exercise may accumulate in the gastrointestinal tract to significant levels [16, 17] which could initiate the vomiting reflex either via stimulation of vagal afferents or through systemic activation of area postrema [18, 19].

An additional 23 patients from the pheochromocytoma/paraganglioma protocol at the NIH were found to experience nausea and/or vomiting though not related to exercise. In these patients, nausea and/or vomiting was elicited during a "spell" or "episode" which could be associated with high blood pressure, heart palpitations, and/or diaphoresis. Importantly, these patients experienced nausea and/or vomiting in a random manner with the sign/symptom occurring during a "spell." This is in contrast to patients with exercise-induced nausea and vomiting, who experienced both events on physical activity which became more frequent and could be elicited with light exercise.

Some patients, who did not experience exercise-induced nausea and vomiting, did suffer from nausea and/or vomiting upon tumor palpation including abdominal massage or on micturition in cases of patients with urinary bladder tumors. If tumor palpation results in the release of catecholamines from the tumor and "spells" are associated with excess catecholamine release, then our hypothesis that nausea and vomiting are elicited from the stimulation of α_1- and α_2-adrenergic receptors may still apply. Questions remain as to why some patients experience nausea and vomiting on exercise while others do not, and why some patients experience nausea and/or vomiting when not exercising.

The 4.4% of all pheochromocytoma/paraganglioma patients experiencing exercise-induced nausea and vomiting at first presentation of pheochromocytoma/paraganglioma may be an underestimation given that all the patients evaluated were not asked to report their exercise level. Furthermore, it is not known how many patients did not exercise at all and thus would not have reported the sign/symptom. Therefore, it is important that clinicians begin asking pheochromocytoma/paraganglioma patients if they have ever had experiences with exercise-induced nausea and vomiting. Patients should also be made aware of the correlation between pheochromocytoma/paraganglioma and exercise-induced nausea and vomiting.

We conclude that exercise-induced nausea and vomiting could be considered a potential sign/symptom of pheochromocytoma/paraganglioma and should be taken into account during clinical evaluation.

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