Published in final edited form as:

Endocrine. 2010 June ; 37(3): 403–407. doi:10.1007/s12020-010-9319-3.

Exercise Induced Nausea and Vomiting: Another Sign of Pheochromocytoma and Paraganglioma Preferably in Young Patients?

Kathryn S. King¹, Nissar Darmani², Karen T. Adams¹, and Karel Pacak¹

¹Reproductive and Adult Endocrinology Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA

²Department of Basic Medical Sciences and Research, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, California 91766, USA

Abstract

Objective—A cohort of nine patients, mostly young adults, presented with a new symptom of pheochromocytoma/paraganglioma: exercise induced nausea and vomiting. The aim of this report is to present this symptom of pheochromocytoma/paraganglioma and to suggest a hypothesis for the observation.

Design—This is a prospective study looking at the patient accounts of the reported symptom and the clinical data on the patients disease.

Methods—Following a 2000 report from a paraganglioma patient of the experience of exercise induced nausea and vomiting, researchers and clinicians at the National Institutes of Health (NIH), pheochromocytoma/paraganglioma protocol, began asking patients about instances of nausea and vomiting induced through exercise. A cohort of nine patients reporting exercise induced nausea and vomiting was found and their clinical data are analyzed and presented here.

Results—Exercise induced nausea and vomiting in pheochromocytoma/paraganglioma patients is most likely due to the elevation of circulating catecholamines that activate adrenergic receptors of the area postrema, which induces nausea and vomiting. Succinate dehydrogenase subunit B mutations/deletions were prevalent in the patients described.

Conclusions—Post exercise nausea and vomiting should be considered as a symptom of pheochromocytoma/paraganglioma and should be addressed in the clinical evaluation of these patients, especially in young adults.

Corresponding author: Karel Pacak, M.D., Ph.D., D.Sc., Chief, Section on Medical Neuroendocrinology, Professor of Medicine, Reproductive and Adult Endocrinology Program, NICHD, NIH Building 10, CRC, 1-East, Room 1-3140, 10 Center Drive, MSC-1109, Bethesda, Maryland 20892-1109, karel@mail.nih.gov, Fax: 1-301-402-0884, Phone: 1-301-402-4594.

DISCLOSURE STATEMENT: The authors have nothing to disclose.

Declaration of Interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Key Terms

Nausea; vomiting; pheochromocytoma; paraganglioma; norepinephrine; epinephrine; catecholamine

Introduction

Pheochromocytomas and paragangliomas, defined as catecholamine producing tumors of the sympathetic or parasympathetic ganglia, are typically diagnosed based on the measurements of catecholamines and their metabolites in the blood and/or urine¹⁻³. The clinical manifestation of pheochromocytoma/paraganglioma is typically characterized by symptoms of elevated blood pressure, heart palpitations, increased perspiration, and anxiety⁴⁻⁶. In 2000 a 23-year-old male patient presented to the National Institutes of Health (NIH) for suspected pheochromocytoma/paraganglioma. While taking a history on the patient it was discovered that 3 years prior, around age 20, he began experiencing episodes of nausea during exercise, especially jogging and lifting weights, which would cause him to discontinue exercise and on cessation of exercise the patient would experience an episode of vomiting. He reported these symptoms becoming worse over the years to the point where he would, starting at age 22, vomit every time he exercised, even when exercise was considered light, such as brisk walking. Following the removal of the patients' primary abdominal tumor symptoms of exercise nausea and vomiting ceased and the patient has been free of these symptoms since. Subsequent to the report of this patient, physicians at the NIH began asking patients about experiences with nausea during exercise and vomiting after exercise. Through this investigation we have discovered a cohort of 9 pheochromocytoma/paraganglioma patients, in total, who initially presented with exercise induced nausea and vomiting. We hypothesize that additional elevation of catecholamines in the blood due to exercise induces nausea and vomiting by activation of α -adrenergic receptors in the brain.

Subjects and Methods

All patients studied here initially presented with both nausea and vomiting. The level of activity that induced this symptom ranged from light to intense, as defined by the CDC and ACSM guidelines, with activities such as biking and swimming (Table 1). During, and following, physical activity these patients experienced the classical pheochromocytoma/paraganglioma symptoms of elevated blood pressure, heart palpitations, profuse sweating, and, in some cases, headaches but they also concomitantly experienced nausea during exercise followed by vomiting at cessation of exercise. The patients studied were all adequately conditioned with the adults reporting having been exercising regularly until the symptoms started and with the parents of the children stating that the children had been very active prior to the reported symptoms. The majority of patients stated that the symptoms of nausea and vomiting grew worse as time went on and that the symptoms could eventually be elicited during instances of light exercise such as carrying a suitcase or picking up a child. Some patients reported that they eventually 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 tumor symptoms of exercise induced nausea and vomiting ceased (Table 1).

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.

Results

Interestingly, patients with metastatic lesions in the organs, such as the lungs in patients 1 and 6, reported a recurrence of exercise induced nausea and vomiting following the development of metastatic tumors. Patients with metastatic lesions solely in the bones, however, did not report a recurrence of exercise induced nausea and vomiting. The extent of the bone lesions in patients 3 and 5 has inhibited these patients from the moderate to intense level of exercise that previously brought about the symptom of nausea and vomiting, thus explaining the disappearance of the symptom despite elevated catecholamine levels. The catecholamine levels in patients 2 and 4, who have metastatic bone lesions, were relatively low which could also account for the absence of nausea and vomiting on exercise.

Characteristics of our patients (Table 2) varied with the mean age of symptom onset being 19.9 years (range: 9–51 years) and the average age of a diagnosis being 23.8 years (range: 11–53 years). Six of our eight patients developed metastatic disease with the average age between diagnosis of pheochromocytoma/paraganglioma and metastatic disease being 4.6 years (range: 0–13 years). Biochemical data (patients gave informed consent prior to any testing at the National Institutes of Health) (Table 3) for the eight patients shows both noradrenergic and adrenergic tumor phenotype. Elevation of normetanephrine levels was common among all patients and elevation of norepinephrine was seen in all patients but one, patient 8, whose norepinephrine levels were elevated immediately prior to admission to the National Institutes of Health. Six of the eight patients studied are known to have mutations/deletions in the succinate dehydrogenase subunit B (SDHB) gene (three of those patients knew about their genetic mutation before presentation at the NIH); the other two patients were not found to have any currently known pheochromocytoma/paraganglioma causing genetic mutations. Our group at the NIH has evaluated approximately 81 patients with SDHB related pheochromocytomas/paragangliomas, 6 of those patients, 7.4%, reported symptoms of exercise induced nausea and vomiting, this is in contrast to the 1.6% of patients without an SDHB mutation or deletion who reported exercise induced nausea and vomiting. Of all the patients evaluated at the NIH with pheochromocytoma/paraganglioma, regardless of genetic status, 3.9% have exhibited symptoms of exercise induced nausea and vomiting.

Discussion

The early age of onset, noradrenergic biochemical phenotype, genetic mutation, and extraadrenal location of the primary tumor among these patients suggests that exercise induced nausea and vomiting may be an important symptom for 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 on the brain stem, by catecholamines such as norepinephrine could be responsible for the nausea and vomiting exhibited in the above-mentioned patients⁷. The area postrema is a circumventricular organ that is not protected by the blood brain barrier and thus is accessible to compounds circulating in the blood⁸, such as catecholamines in a pheochromocytoma/paraganglioma patient. 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 antagonists⁷. Moreover, direct injection of norepinephrine and epinephrine into the third and the lateral ventricle (injection into the fourth ventricle was not preformed) has been shown to induce emesis through activation of α_1 - and α_2 -adrenergic receptors located in the chemoreceptor zone of the fourth ventricle⁹. We propose that the act of exercising increases the amount of circulating catecholamines in pheochromocytoma/paraganglioma patients and may potentially lead to activation of the α_1 - and α_2 -adrenergic receptors in the area postrema inducing nausea and vomiting.

In clinical practice low doses of clonidine is 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^{10, 11}. 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 inducer^{12–14}. This is based on the hypothesis that clonidine acts as a sedative and in the reduction of noradrenergic activity¹². The combination of these two effects by clonidine's action on the presynaptic α_2 -adrenergic receptors is thought to lead to its antiemetic nature¹². On the other hand, activation of postsynaptic α_2 -adrenoceptors by large doses of catecholamines present in pheochromocytoma/paraganglioma patients could lead to emesis.

A large cohort of the patients in this study, six of the eight, has mutations or deletions in the SDHB gene, three (50%) of these patients were aware of their genetic mutation prior to their presentation at the NIH (the other three were diagnosed through testing at the NIH). Seven percent of all patients with SDHB-related pheochromocytoma/paraganglioma evaluated by our group have presented with symptoms of exercise induced nausea and vomiting, this is in contrast to 1.6% of patients with a pheochromocytoma/paraganglioma but no SDHB mutation or deletion who experienced exercise induced nausea and vomiting. SDHB associated pheochromocytomas/paragangliomas are characterized by high malignancy rates, primary tumors occurring in the abdomen and elevated norepinephrine levels in the blood and urine^{15, 16}. If nausea and vomiting were due to activation of α_1 - and α_2 -adrenergic receptors preferably by excess of norepinephrine, patients with SDHB gene mutations and deletions would likely exhibit such symptoms. However, whether these tumors secrete other compounds that could further contribute to nausea and vomiting is currently unknown. Those compounds could include emetic neurotransmitters such as serotonin, dopamine and/or substance P or other compounds^{17, 18}. The noradrenergic phenotype and, perhaps, other currently unknown biochemical characteristics of the SDHB related tumors of pheochromocytoma/paraganglioma patients indicate a distinct possibility for the

development of exercise induced nausea and vomiting and thus could be another clinical characteristic of these tumors. Further evaluation of the pathogenesis of exercise induced nausea and vomiting in SDHB patients should be undertaken with specific investigation into the role of catecholamines and metanephrines in the emetic response.

We cannot exclude bias with this article as we function as a tertiary care center specializing in pheochromocytoma/paranglioma and see a large number of SDHB patients.

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

Acknowledgments

We would like to acknowledge the advice and suggestions provided by Professor Miklos Palkovits, M.D., Ph.D., D.Sc., in the preparation of this manuscript.

Funding: This research was supported, in part, by the Intramural Research Program of the NIH, NICHD.

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Table 1

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 – 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 no yet had primary tumor removed and symptoms are still occurring	HA, palpitations, sweating
9	Biking	Moderate – 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 continue to have symptoms of nausea and vomiting on exercise.

Abbreviations: HA = headache; HTN = hypertension; Pt = patient.

Table 2

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*	51	53	No Meta diagnosis	F	No known mutation	EPI + NMN + MN

Biochemical phenotype data comes from the first plasma catecholamine and metanephrine test performed on the patient at the National Institutes of Health (NIH). (*) Biochemistry tests in patient number 8 prior to testing at the NIH demonstrated elevated norepinephrine levels.

Abbreviations: 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; Meta = Metastatic; MN = Metanephrine; NE = Norepinephrine; NMN = Normetanephrine; Pt = Patient.

Table 3

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*	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 that from the first biochemical test performed on the patients at the National Institutes of Health (NIH). (?) Some of the older patients did not have dopamine or chromogranin A measured. (*) The patient showed elevated norepinephrine levels immediately prior to admission to the NIH.

Abbreviations: 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.