Anesthesia Care Implications of Paragangliomas and Pheochromocytomas

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4/10/2017

Abstract

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare conditions that an anesthesia provider may or may not encounter in his or her career. However, due to the life-threatening nature of these conditions and the critical anesthetic implications in the perioperative periods, the authors deemed it a must to present a lecture to the group of student registered nurse anesthetists (SRNAs) at Adventist University of Health Sciences. The educational lecture was provided with the goal of bridging the SRNAs' knowledge gaps regarding PHEO and PGL in general, and of helping them to be more familiar with PGL in particular.

A convenience sample of 34 SRNAs was utilized after informed consents were obtained. For the purpose of analyzing the effectiveness of the PowerPoint lecture, the pre-test and post-test scores were compared. A paired t test revealed p value of < 0.05, affirming the statistical significance. The pre-test scores had shown the lack of knowledge in general, as evidenced by the low average test scores (3.47/11). The mean post-test scores (6.32/11) were definitely improved after the lecture, albeit the average was still less than optimally anticipated.

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Problem

Pheochromocytoma (PHEO) is a well-recognized term for an adrenal tumor that secretes excessive amount of catecholamine leading to hypertensive issues. What might not be as well recognized is the term Paragangliomas (PGL). PGL and PHEO are rare tumors that are histologically identical but are not always clinically the same (Abdel-Aziz et al., 2015). One of the problems identified for this scholarly project is, defining exactly what PHEO and PGL are and the implications of these tumors on anesthesia care during the perioperative period.

Surgical removal of PGL and PHEO are an infrequent occurrence in an anesthesia provider's career, yet the resection of these tumors can be life threatening making it a must for anesthesia providers to be knowledgeable in the management of the peri-operative period. A direct anesthesia provider, like the student registered nurse anesthetist (SRNA), may or may not come in contact with patients suffering from these conditions during his or her clinical rotations. The aforementioned issue leads to the second problem identified for this scholarly project, why does the SRNA need to know about PGL and PHEO. Owing to the critical hemodynamic fluctuations associated with catecholamine surges and the catastrophic potential, it is imperative for SRNAs to be familiar with anatomy and pathophysiology, clinical presentations, perioperative medical and anesthetic management options, and the different surgical treatment approaches. Due to the rarity and the potential of life threatening events related to PGL and PHEO resection, the SRNA needs to be able to provide quality care during these surgical cases. Thus, a forty-five-minute PowerPoint presentation was given to the Adventist University of Health Science's (ADU) nurse anesthesia program (NAP) SRNA classes of 2017 and 2018 cohorts, also a pre and post-test was given with the expectation that the post-test would have a higher score showing an increase in the SRNAs' knowledge base.

Review of Literature

Paraganglioma is the umbrella term for the rare tumors arising from the neural crest chromaffin tissues of the sympathetic and parasympathetic nervous systems (King and Pacak, 2014). PGL is also interchangeably called extra-adrenal pheochromocytoma. Due to the involvement of both nervous systems, PGL can be found anywhere along the ganglia (group of nerve cells), from the carotid body on the neck all the way down to the epididymis. A type of paraganglioma is PHEO, but the term is designated exclusively for the tumors of the adrenal medulla, which can be unilateral (approximately 90% of the cases) or bilateral (10%) (Renard, Clerici, Licker, Triponez, 2011). About 90% of PGLs are found in the abdomen "along the aorta from just above the level of the renal hilum to the aortic bifurcation" (Goers et al., 2013, p. 428). Abdominal PHEO and PGL are usually functioning in terms of catecholamine secretion but could be asymptomatic. There is inconsistent data on the prevalence of PHEO according to the literature review, which is ranging from as high as 1 in 2000 people, per Miller and Pardo (2011), to 2 - 8 in a million people per year according to 2015 National Cancer Institute report. According to Abdel-Aziz et al. (2015) the incidence of combined PHEO and PGL is 0.2 per million for pediatric patients and 2 per million for adults.

Current literature of PHEO and PGL focus on recognizing the clinical signs and symptoms, diagnostic laboratory tests, imaging studies, and treatment modalities. The treatment modalities include such things as medical management and surgical options, as well as, the prognosis and survival rates with or without interventions. Current literature also looks at some hereditary connections of at least thirteen identified mutated genes with other neuroendocrine tumors and the study of the malignant forms of PHEO and PGL.

Conventionally, PHEO was known to be the "tumor of 10%: 10% are bilateral, 10% are malignant, 10% are extra adrenal, 10% are diagnosed in asymptomatic patients and 10% are hereditary" (Renard et al., 2011, p. 410). Although there are questions about these statistics' validity in recent years, they give general ideas about PHEO as a starting point. However, early identification of PHEO signs and symptoms are imperative for the anesthesia clinician.

Classic triad symptoms are "recurrent headaches, profuse perspiration and palpitation" (Renard et al., 2011, p. 410). Other symptoms may include extremely labile blood pressure out of proportion to usual anesthesia or surgery related stimuli, orthostatic changes, chest discomfort, EKG changes, elevated serum glucose levels, nausea/vomiting, and anxiety attacks. However, these symptoms can be non-specific or absent, making the accurate diagnosis quite challenging.

A sudden surge of massive amounts of catecholamine can lead to a "storm". Without effective and timely interventions, complications like uncontrolled high blood pressure, spasm of the coronary arteries, irregular heart rhythms, weakened heart muscles, cerebral infarct, and pulmonary edema are inevitable, increasing the morbidity and mortality rates (Renard et al., 2011). Alpha-adrenergic receptor blockade by phenoxybenzamine has been the treatment of choice to optimize patient's blood pressure preoperatively. Other α_1-blockade agents such as prazosin can be given with the caution for orthostatic hypotension. Beta blockers are to be initiated only after adequate α-blockade is achieved to prevent unhindered α stimulation (Jaffe, Schmiesing, and Golianu, 2014).

Increased salt and water excretion in response to chronically elevated blood pressure can lead to intravascular volume depletion, which may be compounded by patient's diuretic use. After the removal of the tumor, patient can suffer from profound hypotension refractory to adrenergic agonist administration. However, the morbidity and mortality rates over the past 50

plus years have significantly gone down from 40 - 60% to 0 - 6% thanks to the careful perioperative blood pressure management with various antihypertensive medications and the prevention of cardiac arrhythmia with fluid management post tumor removal. (Renard et al., 2011)

The same study by Renard et al. (2011) goes on to say, although medical management strategies for PHEO and PGL have done their parts, they are considered a "palliative option" at best. The best treatment option, so far, is considered to be the surgical removal of the tumor. Ever since Cesar Roux removed the first PHEO successfully in 1929, there has been tremendous improvement in the surgical approaches. Nowadays, laparoscopic adrenalectomy either transperitoneally or retroperitoneally is considered the norm for PHEO removal. When the tumor size is too big, an open approach can be utilized via subcostal vs. vertical midline laparotomy, though subcostal approach is preferred. Extremely large tumor requires thoraco-phreno-laparotomy approach from the right side. (Renard et al., 2011)

Unilateral total adrenalectomy is the treatment of choice for sporadic or unilateral PHEO, while bilateral adrenalectomy is reserved only for bilateral PHEO. After bilateral adrenalectomy, secondary adrenal insufficiency is of concern leading to lifetime steroid replacement therapy. Usually, the tumor is resected with a small portion of the left adrenal gland, to allow cortical function. However, due to the close proximity of the adrenal cortex and the medulla, risk for tumor recurrence needs to be considered. Malignant PHEO is treated with the similar course of surgical interventions, performed with more open approaches in order to remove adjacent organs along with the tumor, and then followed by chemo and radiation therapy. Abdominal PGL surgeries usually involve the organ of Zuckerkandl, which has rich arterial supplies including the aorta and its bifurcation, thus, representing more challenges. Routine

prophylactic lymph node removal is controversial with no strong scientific support. However, the possibility of 30% malignancy in sporadic PGL should not be neglected by the operating surgeons. (Renard et al., 2011)

Anesthetic considerations in regards to PHEO and PGL removal include regional alone or regional plus general endotracheal anesthesia (GETA). (Renard et al., 2011). However, Jaffe et al. (2014) only mentioned GETA for both laparoscopic and open procedures. Epidural for postoperative pain management is a must for open surgical approach (Renard et al., 2011; Jaffe et al., 2014). Due to exaggerated hemodynamic fluctuations, arterial line placement is necessary along with the basic American Society of Anesthesiologist (ASA) recommended intraoperative monitoring. Cardiac defibrillator and emergency vasoactive drugs should be readily available with the goal of heart rate less than 80 beats per minute and mean arterial pressure of 80-100 mmHg (Renard et al., 2011). Perioperative volume status is an important indicator of hemodynamic stability; therefore, intraoperative transesophageal echocardiogram, noninvasive arterial pressure monitoring device, to estimate the stroke volume, and/or a pulmonary artery catheter should be used.

In an effort to prevent sympathetic stimulation from direct laryngoscopy, a deeper level of anesthesia needs to be ensured. Muscle relaxation via bolus or infusion is required. During tumor manipulation, the anesthesia provider needs to have close control of tachyarrhythmia and hypertension. It may be necessary for the surgeon to stop manipulating the tumor temporarily for better hemodynamic control (Jaffe et al., 2014). Once the tumor is excised, the patient can experience profound hypotension due to catecholamine depletion, which may necessitate administration of sympathomimetic drugs and fluid resuscitation. Phenylephrine may not be effective if residual α-blockade persists from the preoperative regimen (Jaffe et al., 2014).

Perioperative glucose monitoring is as important as hemodynamic monitoring due to significant fluctuations in blood sugar before and after the tumor removal. Classic symptoms of hypoglycemia perioperatively can be masked easily by the anesthetic agents and opioids. Undetected hypoglycemia can lead to loss of consciousness and respiratory arrest in severe cases. (Renard et al., 2011)

As above, the current literature review has revealed well-established data on PHEO in terms of pathophysiology, hereditary factors and connection to other gene mutations and neuroendocrine conditions, diagnostic tools, perioperative medical/anesthetic management, and surgical approaches. However, there are limited amounts of information on PGL in general due to the rare incidence rates and the lack of consistency in disease presentation in contrast to PHEO which is exclusive to adrenal glands only. Literature on PGL were more focused on the case studies revolving around the various ganglia involved and the majority of them were related to abdominal paraganglioma with similar management approaches to PHEO. Therefore, the purpose of this capstone project was to provide SRNAs with an in-depth foundation of knowledge related to PHEO and PGL anesthetic management in conjunction with bringing more consideration to PGLs.

Project Description

The goal of this scholarly project is to increase the knowledge base of SRNAs at Adventist University of Health Science's (ADU) nurse anesthesia program (NAP) as it pertains to PGL and PHEO by presenting a PowerPoint to the ADU's NAP students. The PowerPoint presentation was given in the fall of 2016 in the MSNA 501 and 504 class to cohorts of 2017 and 2018 graduating classes. These cohorts of the NAP were utilized as a convenience sample of 34 subjects.

This research project, *Anesthesia Care Implications of Paragangliomas and Pheochromocytomas*, has been determined to be Exempt from review by the Institutional Review Board (IRB) at ADU as defined by regulations. However, this research project has received Scientific Review Committee (SRC) approval by the ADU Research Office. The IRB and the SRC determine and ensure that the subjects have not had undue risk, and ensure that all safety and legal requirements have been met and that the appropriate forms have been completed.

The subjects were given an informed consent, provided by the principal investigators, that the subjects signed prior to the pre-test. Once consent was obtained, the subjects were handed a pre-test to complete and hand back to the investigators before the lecture was presented. Upon completion of the forty-five-minute lecture using a PowerPoint, the subjects completed a post-test, provided by the principal investigators. The post-test had the same exact questions as the pre-test the subjects took before the lecture. Both the pre- and post-test had a numbering system and was returned to the investigators in a random format to allow for the subjects' anonymity.

A poster highlighting the main points of the *Anesthesia Care Implications of Paragangliomas and Pheochromocytomas* scholarly project was accessible to the public during the annual Capstone Project Poster presentation. During this poster presentation the primary investigators were available to answer questions. The poster features the results of the pre- and post-test, validating the effectiveness of this project by statistical significance of the data.

Evaluation Plan

Once the Anesthesia Care Implications of Paragangliomas and Pheochromocytomas project was submitted to ADU Scientific Review Committee (SRC) and Institutional Review Board (IRB), with the approvals received, the lecture was presented to the 2017 and 2018 NAP

cohorts. Using a quantitative study design this scholarly project utilized a pre- and post-test as the measure to determine if the lecture had improved the NAP students' knowledge base on the anesthesia care implications of PGL and PHEO. The pre- and post-tests was analyzed using the SPSS program by Dr. Roy Lukman. A simple paired t-test was utilized to compare the pre- and post-test scores, measuring the effectiveness of the PowerPoint presentation. The purpose of this scholarly project is to increase the SRNAs' knowledge of PGL and PHEO. The project's goal, increasing the SRNAs' comprehension of PGL and PHEO with the PowerPoint presentation, will was deemed successful, because there is a significant statistical (*p*-value - 0.000) improvement in the post-test scores after the PowerPoint presentation, compared to the pre-test.

Results and Conclusions

A pre-test was given to 34 subjects prior to the PowerPoint presentation that had the objectives of the learners being able to: tell the similarities and the differences between PGL and PHEO, verbalize the anatomy and physiology of PGL and PHEO, recognize the major genetic mutations associated with PGL and PHEO, name the classic triad symptoms of PGL and PHEO, tell the diagnostic tools for PGL and PHEO, and develop an anesthetic plan. After the educational PowerPoint presentation, the subjects then received a post-test that was identical to the pre-test. The data was collected by the researchers and sent to Dr. Roy Lukman for analysis. See the tables below for details of the results.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-Test - Post-Test	-2.85294	2.37579	.40744	-3.68189	-2.02399	-7.002	33	.000

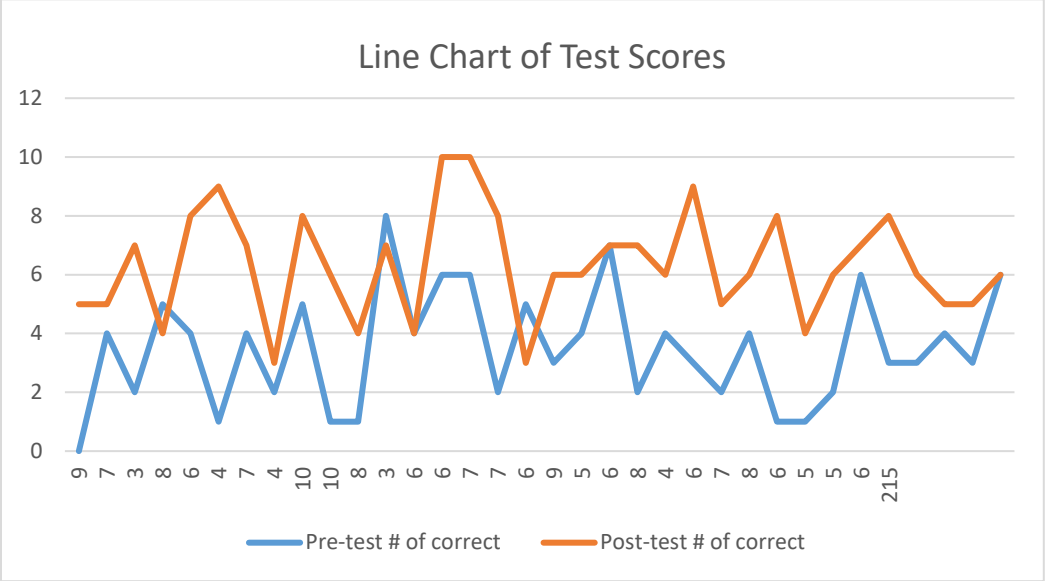
Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-Test	3.4706	34	1.94212	.33307
	Post-Test	6.3235	34	1.83766	.31516

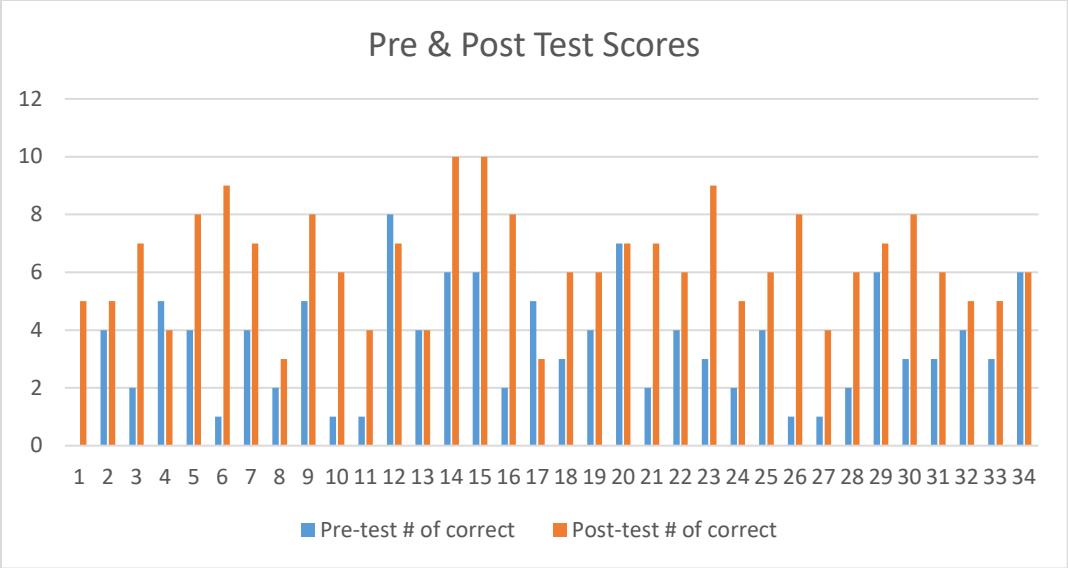
The analysis of data was carried out by performing a paired sample *t*-test in SPSS. Of the 34 subjects the mean pre-test score was 3.47 and the post-test was near doubled with a mean score of 6.32 out of 11 questions. Statistical significance was claimed by the researchers as a *p*-value less than 0.5, as shown in the table the p-value was 0.000, ensuring approximately 95% confidence interval (*CI* -3.68, -2.02) in the results. An upper-tailed and lower-tailed hypothesis was used to increase the power of the test ($p = 0.00$) showing there is strong evidence that, on average, the educational PowerPoint presentation leads to improved post-test scores. The analysis above supports the researchers' hypothesis that the subjects would gain knowledge of PHEO and PGL after listening to the lecture and viewing the PowerPoint.

Surprisingly, the scores were low in the pre-test, presenting a large lack of knowledge on PHEO and PGL. The convenience sample group was made up of both first year and second year nurse anesthesia students. The researchers did not separate the first year students from the second year students, which might skew the results. There is a possibility that there were more first year students in the sample group than second year students and most likely these students

would not have had a class with the topic of PHEO or PGL, causing lower scores. Furthermore, the post-test mean score (6.32/11) is low as well leading the researchers to believe the test might need to be reworded or better reflect the lecture than it currently does.



Another weakness of this project was the fact that the sample group was selected in convenience. These students were in a classroom setting after a full day of clinical work in the hospital, possibly leading to fatigue in the sample group. This group was required to be in class, not necessarily needing to participate in the research project, but they might have felt pressured to be in the sample group yet not have the mind set of trying their hardest to learn the material. However, the statistical significance does show the project's expectation of, the post-test having a higher score, confirming an increase in the SRNAs' knowledge. Therefore, the goal of the project has been met.



The clinical implications of this research project would be to present the PowerPoint education to future nurse anesthesia students, so they may gain knowledge of PHEO and PGL. Allowing the student nurse anesthetist to be better prepared for the possibility of caring for a rare yet potentially life threatening event in the operating room. The knowledge gained by the nurse anesthesia students can then be passed onto their preceptors in the clinical settings, thus growing the body of knowledge across the nurse anesthesia community. Since the education has shown statistical significance in increasing PHEO and PGL knowledge in those exposed, using this education will be helpful for current certified registered nurse anesthetists has a continuing education module or presentation.

References

Abdel-Aziz, T. E., Prete, F., Conway, G., Gaze, M., Bomanji, J., Bouloux, P., ... Kurzawinski, T. R. (2015). Pheochromocytomas and paragangliomas: A difference in disease behaviour and clinical outcomes. *Journal of Surgical Oncology*, *112*, 486-491. http://dx.doi.org /10.1002/jso.24030

Goers, T. A., Abdo, M., Moley, J. F., Matthews, B. D., Quasebarth, M., & Brunt, L. M. (2013). Outcomes of resection of extra-adrenal pheochromocytomas/paragangliomas in the laparoscopic era: A comparison with adrenal pheochromocytoma. *Surg Endosc*, *27*, 428-433. http://dx.doi.org/10.1007/s00464-012-2451-9

Jaffe, R. A., Schmiesing, C. A., & Golianu, B. (2014). *Anesthesiologist's manual of surgical procedures* (5th ed.). Philadelphia, PA: Wolters Kluwer Health.

King, K. S., & Pacak, K. (2014). Familial pheochromocytomas and paragangliomas. *Molecular and Cellular Endocrinology*, *386*, 92-100. http://dx.doi.org/10.1016/j.mce.2013.07.032

Miller, R. D., & Pardo, M. C. (2011). *Basics of Anesthesia* (6th ed.). Philadelphia, PA: Elsevier Saunders.

Pheochromocytoma and paraganglioma treatment (PDQ) - health professional version. (2015). Retrieved June 5, 2016, from cancer.gov/types/pheochromocytoma/hp/pheochromo cytoma-treatment-pdq

Renard, J., Clerici, T., Licker, M., & Triponez, F. (2011). Pheochromocytoma and abdominal paraganglioma. *Journal of Visceral Surgery*, *148*, 409-416. http://dx.doi.org/10.1016/ j.jviscsurg.2011.07.003

Appendix A

Anesthesia Care Implications of Paragangliomas and Pheochromocytomas

Survey Questions – Answers
Pre- and Post-Test

1. How are Paragangliomas and Pheochromocytomas related?
    - **a. Arise from the neural crest**
    - b. Both always emit catecholamine
    - c. Both are always seen in the abdominal region of the patient
    - d. All of the above

2. Pheochromocytomas are…
    - a. Always a non-cancerous tumor
    - **b. A rare tumor of the adrenal medulla**
    - c. A tumor mainly found in men
    - d. All of the above

3. Pheochromocytomas are functionally active tumors secreting?
    - a. Epinephrine, serotonin, dopamine
    - **b. Norepinephrine, epinephrine, and sometimes dopamine**
    - c. Norepinephrine, epinephrine and sometimes cortisol
    - d. All of the above

4. The preoperative anesthesia goal for pheochromocytoma and functioning paraganglioma is to…
    - a. Initially start beta-blockers to control hypertension
    - b. Use regional anesthesia to decrease the release of catecholamine
    - c. Prepare nitroprusside and ephedrine infusions in advance
    - **d. Control blood pressure and restore the intravascular volume**

5. Which one of these are not considered a “classical symptomatic triad of pheochromocytomas”?
    - a. Recurrent headaches
    - b. Paroxysmal diaphoresis Profuse perspiration
    - **c. Visual blurring**
    - d. Palpitation

6. Which statement is *not true* regarding laboratory diagnosis for PHEO and PGL?
    - a. 24-hour urine collection for measurement of total or fractionated urinary catecholamines and metabolites are considered standard.
    - b. Normetanephrine and metanephrine are measured in the serum and urine, and have a sensitivity and specificity up to 98% and 98%.

   c. **Urine or serum negative test results for catecholamine metabolites are NOT sufficient to rule out PHEO.**
   d. Chromogranin A has low sensitivity for diagnosis of PHEO and PGL, but it can be used as a marker for malignancy and as an easy marker of recurrence for follow-up.

7. Phenoxybenzamine is a drug of choice for pre-operative blood pressure management for PHEO and PGL. Which statement is *not true* about phenoxybenzamine?
   a. **Phenoxybenzamine is a selective α1-blocker**.
   b. Patients are given phenoxybenzamine for a minimum of 2 weeks prior to surgery.
   c. The starting dosage is 10mg/day and it can be increased up to 80mg/day as needed.
   d. The goal of therapy is to maintain a normotensive state and light orthostatic hypotension.
   e. β-blockers should be introduced only after adequate α-blockade is achieved to prevent unhindered α stimulation.

8. Which is not true regarding the surgical management of PHEO and PGL?
   a. Surgical tumor removal is considered the only treatment for all forms of PHEO and PGL.
   b. Currently, most PHEO are removed laparoscopically either transperitoneally or retroperitoneally.
   c. Malignant PHEO is more frequently removed by open approaches than laparoscopically in order to ensure complete surgical excision of malignant tumors.
   d. Chemotherapy and/or radiopharmaceutical therapy often follow the resection of the malignant tumors.

9. Which statement is *not true* about anesthetic management for the patients going through PHEO and PGL removal?
   a. Routine monitoring should include ECG, A-line, capnography, inspired O2 concentration (FiO2), pulse oximetry (SpO2), neuromuscular blockade, and temperature.
   b. Regional anesthesia is more frequently used for this type of surgery than general anesthesia.
   c. Any drugs potentially releasing histamines or catecholamines should be avoided.
   d. HR < 80/min and MAP between 80-100 mmHg are considered as satisfactory hemodynamic profile.
   e. A deeper level of anesthesia should be provided during direct laryngoscopy and intubation in order to prevent a reflex increase in sympathoadrenal activity.

10. Perioperatively, what are the complications related to removal of PHEO and PGL?

a. Extreme swing of BP including intraop hypertension during tumor manipulation by surgeon and postop hypotension
b. Adrenal insufficiency, especially after bilateral adrenalectomy
c. Catecholamine induced intraop hyperglycemia and postop Hypoglycemia within minutes after surgery because α-induced suppression of insulin release has waned.
d. All of the above

11. It has been known that 10-30% of PHEO and PGL have genetic origins. Which one of these conditions are related to PHEO and PGL?
    a. Von Hippel-Lindau (VHL)
    b. Multiple Endocrine Neoplasia type 2 (MEN 2)
    c. Neurofibromatosis type 1 (also called Von Recklinghausen disease, multiple neurofibromatosis, and Café au lait spots)
    d. Syndrome of succinate dehydrogenase (SDHB, SDHD, SDHC, SDHA in order of frequency)
    e. All of the above

Appendix B

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

Our names are Soomee Pak and Mignon Nielsen, and we are MSNA students in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). We are doing a Capstone Project called *Anesthesia Care Implications of Paragangliomas and Pheochromocytomas.* This project is being supervised by Steve Fowler, CRNA, DNP. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to provide the SRNA with a better knowledge base of a rare, but life threatening tumors called Paraganglioma and Pheochromocytoma plus the anesthesia implications.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address your knowledge of Paragangliomas and Pheochromocytomas. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately 60 minutes.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional knowledge that will guide you in developing an effective anesthetic plan of care for patients with Paragangliomas and Pheochromocytomas.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. Each student will be provided with a numbered test that will be used for both the pre- and post-test, instead of using names. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 60 minutes of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigators will be happy to answer any questions you have about the project. If you have any questions, please feel free to contact Soomee Pak at Soomee.Pak@my.adu.edu or Mignon Nielsen at Mignon.Nielsen@my.adu.edu. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

_____ _____

Participant Signature **Date**

_____

Participant Name (PRINTED LEGIBLY)

Appendix C
Analysis Charts

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
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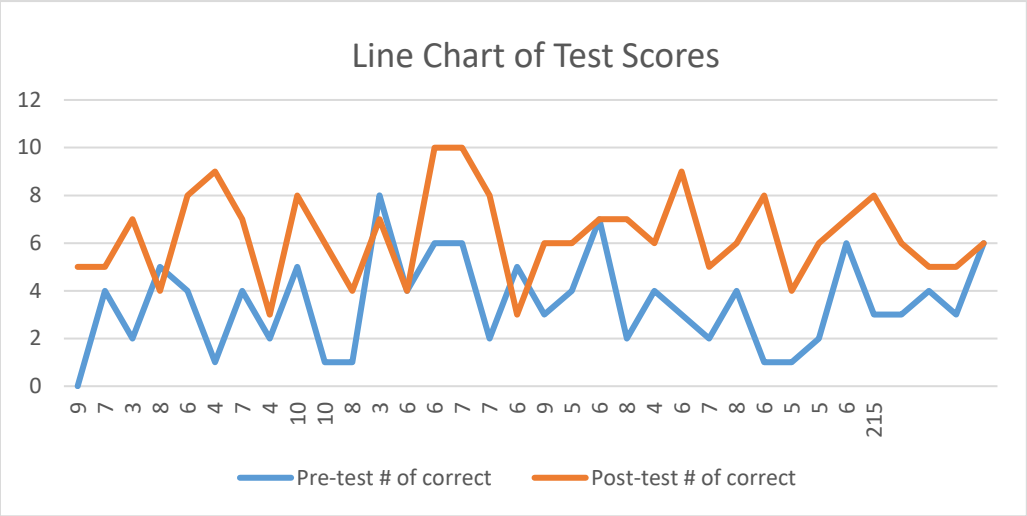
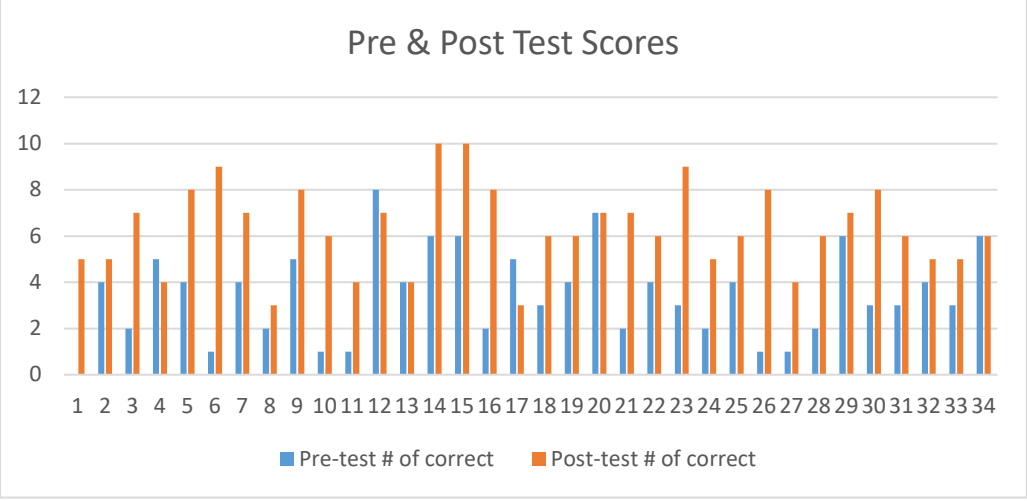




Appendix D
PowerPoint Presentation

Anesthesia Care Implications of Paragangliomas and Pheochromocytomas

Soomee Pak, BSN, RN, SRNA &
Mignon Nielsen BSN, RN, SRNA

Objectives

- After this lecture, the learners will be able to:
  - Tell the similarities and the differences between Paraganglioma (PGL) and Pheochromocytoma (PHEO).
  - Verbalize the anatomy and physiology of PGL and PHEO.
  - Recognize the major genetic mutations associated with PGL and PHEO.
  - Name the classic triad symptoms of PGL and PHEO.
  - Tell the diagnostic tools for PGL and PHEO.
  - Develop an anesthetic plan.

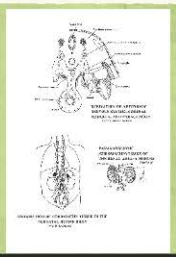
Paraganglioma (PGL) Case

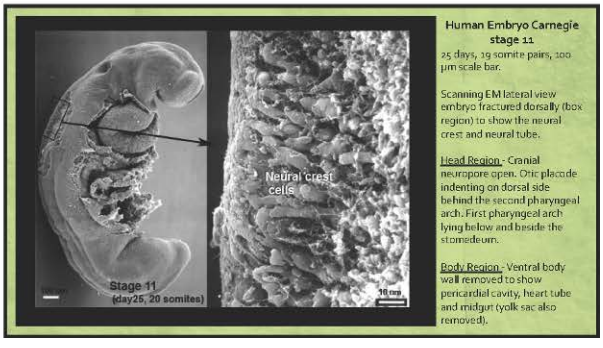
- 42 yo male in Pre-op for excision of PGL
- On interview discovered patient was taking phenoxybenzamine
- No mention of pheochromocytoma (PHEO) in the medical records
- Patient revealed that his paraganglioma was releasing catecholamine and presented with all the same symptoms of PHEO
- He also revealed that his mother had died from her paragangliomas
- Allowed for preparation of the operating room (OR) for potential catastrophe
- PHEO/PGL affecting 1 in 2500-6500 individuals, with 500-1600 new cases diagnosed in US annually (Martucci & Pacak, 2014)

Anatomy & Physiology

Paraganglionic System

- Paraganglia
  - Groups of cells located near ganglia
  - Ganglia – plural for ganglion
    - Nerve cell bodies of the autonomic nervous system
    - Ganglia house the cell bodies of **afferent** nerve fibers
- Develop in early gestation from the neural crest
- In the 2nd month of gestation
  - The sympathogonia detach from sympathetic primordium & differentiate into glandular cells – ***paraganglia***



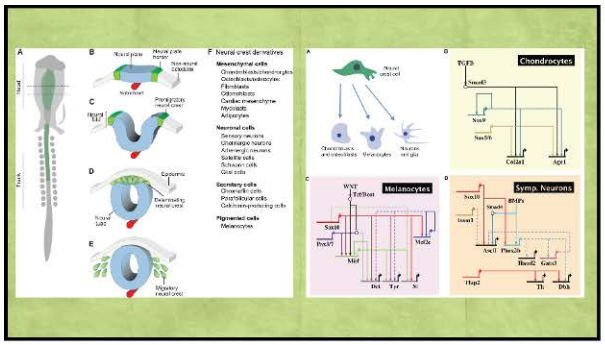


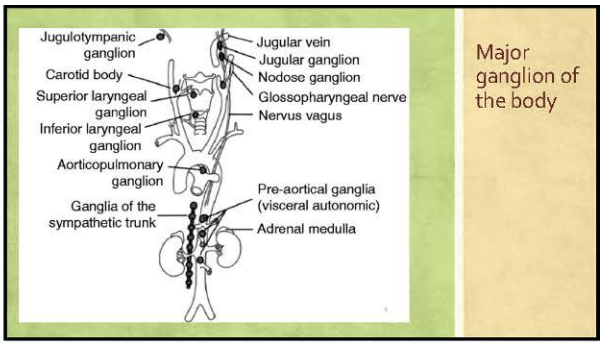
Human Embryo Carnegie stage 11
25 days, 19 somite pairs, 100 µm scale bar.

Scanning EM lateral view embryo fractured dorsally (box region) to show the neural crest and neural tube.

Head Region - Cranial neuropore open. Otic placode indenting on dorsal side behind the second pharyngeal arch. First pharyngeal arch lying below and beside the stomedeum.

Body Region - Ventral body wall removed to show pericardial cavity, heart tube and midgut (yolk sac also removed).





Paraganglionic System

- Chromaffin body system
  - Collection of chromaffin cells
  - Epinephrine (adrenaline) producing paraganglia selectively take up chromium salts = chromaffin reaction
  - Ach secreting cells do not show the same staining reaction as those of the adrenaline-producing paraganglia – no chromaffin reaction
- Function of the paraganglia
  - Secrete epi & norepi
  - Some located near vagus nerve secrete acetylcholine
  - To control fetal BP until adrenal medulla & autonomic nervous system take over
  - May support organs that function continuously like heart and vasosensory system that controls circulation

Paraganglionic System

- These paraganglia regress after birth when the adrenal medulla begins to function
  - i.e. Body of Zuckerkandl
- Two components
  - Adrenal medulla
  - Diffuse collection of extra-adrenal paraganglia
- Paraganglia cells vs. neuroblast
  - Smaller size
  - Characteristic reaction to staining
    - Dichromate salts = yellow
    - Ferric chloride = green
    - dt: presence of cytoplasmic droplets that are the precursors for epi & norepi

What are Paragangliomas?

\

Nomenclatures/Glossaries

- Para (Next to/ besides) + ganglion (a group of nerve cell bodies located in the autonomic nervous system) + oma (tumor)
- Pheo + chrmo + cyte + oma = **Greek** (phaios "dark", chroma "color", kytos "cell", -oma "tumor") = Paraganglioma in the adrenal medulla
- Extraadrenal pheochromocytoma = Paraganglioma
- Functioning = Catecholamine producing
- "Pharmacological time bomb"

Nomenclatures/Glossaries

- Sympathetic paraganglioma:
  - Adrenal medulla (producing Epi and Norepi)
  - **Organ of Zuckerkandl** near the aortic bifurcation (secretes epi)
  - Other paraganglioma along the distribution of the SNS
- Parasympathetic paraganglioma
  - Majority of Head and Neck PGLs (i.e.: carotid body)
  - Other paraganglioma along the cervical and thoracic branches of vagus and glossopharyngeal nerves

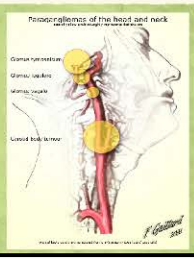
The incidence of combined PHEO and PGL is 0.2 per million for pediatric patients and 2 per million for adults (Abdel-Aziz et al., 2015)

Many faces of Paragangliomas

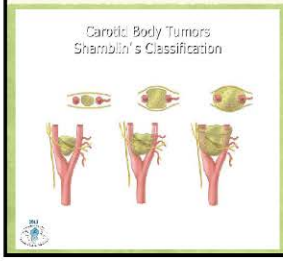
- Head and Neck (3% of all PGLs)
- Thorax/mediastinum (12%)
- Intraabdominal (80-85%)
  - Adrenal
- Bladder (6%)
- Rare sites like epididymis/ paratesticular

Head and Neck Paragangliomas (HNPGL)

- Carotid Body PGL: Along carotid bifurcation
- Glomus tympanicum: small size tumors originating from middle ear space
- Glomus Jugulare: Arise from in or around jugular bulb
- Glomus Vagale: Bet. Jugular vein and ICA, extending to jugular foramen or posterior to the mastoid bone



Carotid Body Tumor (CBT) = Chemodectoma: **Shamblin classification**



- ***Class I***: Localized tumors with splaying of the carotid bifurcation, but little attachment to the carotid vessels. Complete resection with very little morbidity
- ***Class II***: Partially surround the carotid vessels, complete resection is more challenging.
- ***Class III***: Intimately surround the carotid, complete resection is very challenging, and often requires temporary interruption of the cerebral circulation for vascular reconstruction. The risk of permanent vascular and neural defects is significantly higher than for Class I and II.

CBT cont'd

- Complete surgical resection is the only therapeutic option potentially offering a cure for the pt (Treatment of choice).
- Done via a Transcervical approach
- With complete tumor resection, tumor is controlled locally 89-100% of cases.
- Probability of postop CN dysfunction even in cases of successful surgical removal of CBT (Ex: 21.8% permanent CN damage in study by Anand et al.)
- As Shamblin tumor classification increases from I-III, more difficult and challenging surgery becomes.

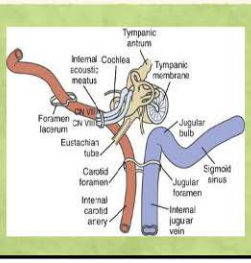
Tympanic PGL = Glomus Tympanicum (TP)

Glomus tympanicum tumor (red mass in bottom of middle ear)

TP: Mostly small sized tumor originating in the middle ear

- Pulsatile tinnitus in the vast majority of pts
- Hearing loss initially in about 50% of pts
- Visible as a vascular middle ear mass
- Dx: careful exam of tympanic membrane and id of tumor through translucent eardrum, CT and MRI

Jugular PGL = Glomus Jugulare (JP)



- JP: Arise from paraganglia in or around the jugular bulb.
  - Occlusion of venous flow as tumor grows
  - Pulsatile tinnitus, bruit over the ear,
  - Conductive hearing loss, then sensorineural hearing loss or dizziness when inner ear is invaded
  - Dysfunctional swallowing and husky voice due to other CN deficits
  - Facial nerve paralysis, paralysis of ½ of tongue (CN IX)
  - Further growth leads to compression of brain and/or brain stem

Temporal Paragangliomas

- **Fisch** classification:

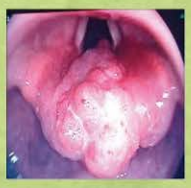
TPs
- A: PGL along the tympanic plexus on promontory
- B: PGL with invasion of hypotympanon, cortical bone over jugular bone intact

JPs
- C1: PGL with erosion of carotid foramen
- C2: PGL with destruction of vertical carotid canal
- C3: PGL with involvement of horizontal portion of carotid canal; foramen lacerum intact
- C4: PGL with invasion of foramen lacerum and cavernous sinus
- De 1/ 2: PGL with intracranial but extradural extension; according to displacement of dura (De1 = <2cm, De2 = < 2cm)
- Di 1/2/3: PGL with intracranial and intradural extension; according to depth of invasion into the posterior cranial fossa (Di1 = <2cm,Di2 = <2-4cm, Di3 = >4cm)

Vagal Paraganglioma (VP)

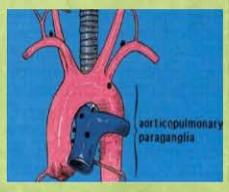
- Located more cephalad in the neck, between jugular vein and ICA, sometimes, extending to jugular foramen or posterior to the mastoid bone
- Arise from glomus nodosum, that is, inferior ganglion
- S/S depends on the location of tumor along the vagal nerve from the skull base to the lower neck
- Asymptomatic neck mass behind the angle of the mandible
- Pulsatile tinnitus or ringing in the ear heard with each heartbeat
- < 50% present with CN deficits: hoarseness (X), dysphagia (IX), shoulder drop (XI), nasal reflux of fluids, aspiration and hemiarthrophy of the tongue (XII), intracranial extension leading to death (22% of cases), bulging of the pharyngeal wall into the pharyngeal lumen, and mediastinal displacement of tonsil

Laryngeal PGL



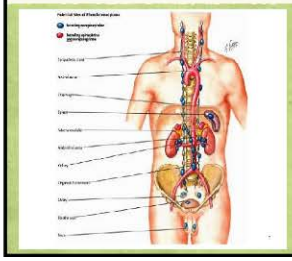
- Arise from superior and inferior paraganglia (SLN and RLN)
- Seen in supraglottic in 90%
- Benign submucosal lesion
- Management: conservative resection (supraglottic laryngectomy, lateral pharyngectomy)
- Sig. intraop blood loss – preop transarterial embolization beneficial

Thorax PGL/ Mediastinal PGL

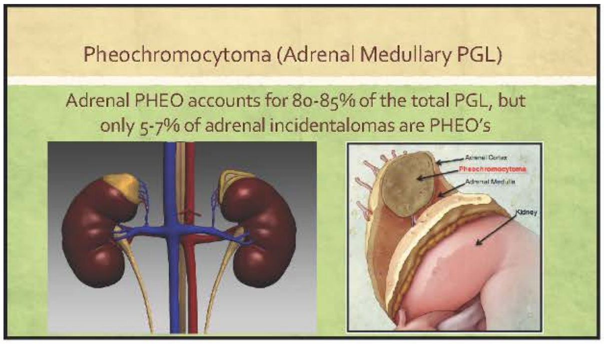


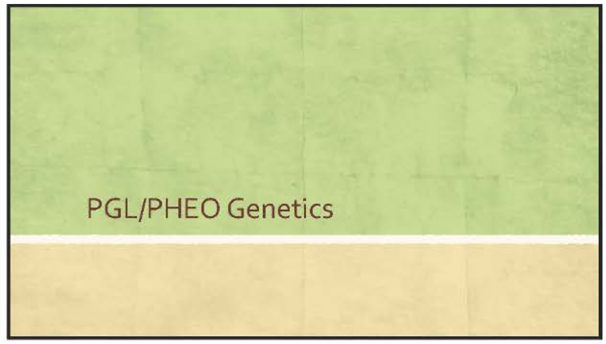
- Arise from chromaffin tissue in Paraaortic or paravertebral ganglia
- Proximal to great vessels, trachea, and RLN
- Up to 50% pts asymptomatic
- Incidental Dx
- S/S: r.t. hypersecretion or mass effect causing hoarseness, dysphagia,SOB,CP
- Complete surgical resection-standard due to malignant potential of the tumor & poor response to chemo & rad.

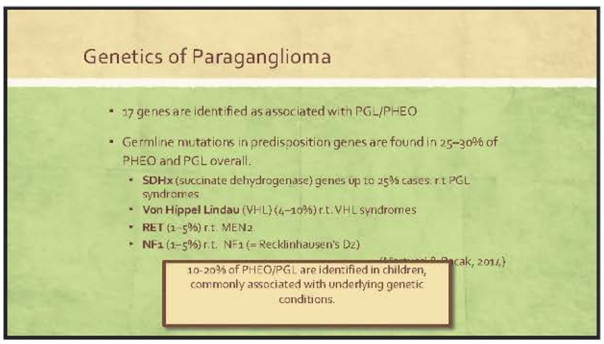
Superior and Inferior Abdominal Paraaortic PGL

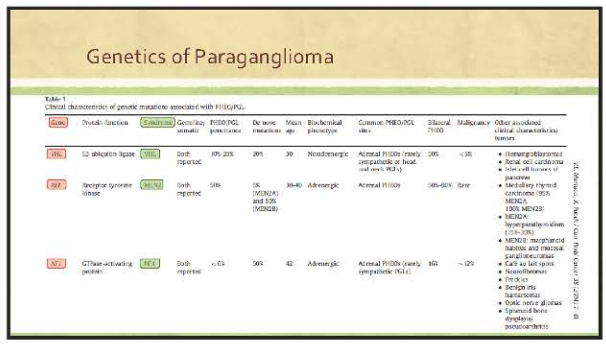


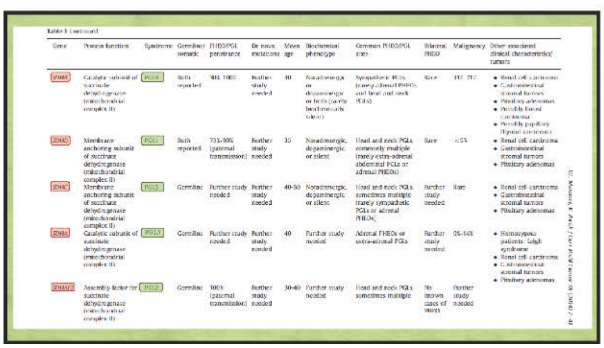
- 90% of extraadrenal PGLs located intraabdominally
- Organ of Zuckerkandl:
  - located at the bifurcation of aorta or at the origin of inferior mesenteric artery
  - Produce adrenaline

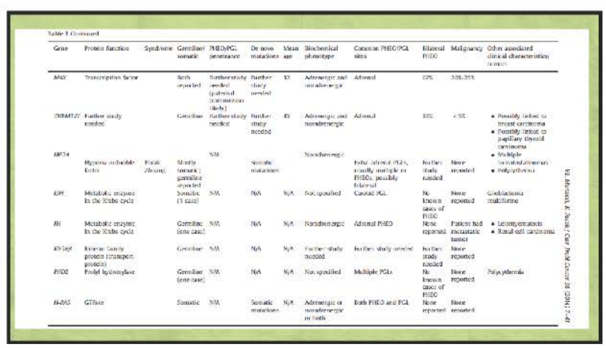

Pheochromocytoma (Adrenal Medullary PGL)
Adrenal PHEO accounts for 80-85% of the total PGL, but only 5-7% of adrenal incidentalomas are PHEO's
Adrenal Cortex
Pheochromocytoma
Adrenal Medulla
Kidney


PGL/PHEO Genetics


Genetics of Paraganglioma
• 17 genes are identified as associated with PGL/PHEO
• Germline mutations in predisposition genes are found in 25–30% of PHEO and PGL overall.
• SDHx (succinate dehydrogenase) genes up to 25% cases: r.t PGL syndromes
• Von Hippel Lindau (VHL) (4–10%) r.t. VHL syndromes
• RET (1–5%) r.t. MEN2
• NF1 (1–5%) r.t. NF1 (= Recklinhausen's Dz)
cak, 2014)
10-20% of PHEO/PGL are identified in children, commonly associated with underlying genetic conditions.


Genetics of Paraganglioma





The president and Pheochromocytoma

(Messerli et al., 2007)

Clinical Manifestations of Catecholamine Releasing PGL & PHEO

Clinical Manifestations of Catecholamine Releasing Paragangliomas & PHEO

- Massive Catecholamine Release
  - HTN
    - Paroxysmal or sustained
  - Diaphoresis
  - HA
  - Tremors
  - Palpitations
- **Triad** s/s for PHEO
  - Hypertensive pt with
    - Paroxysmal diaphoresis, tachycardia, & HA

Rare cause of secondary HTN with incidence in HTN pts of only 0.3-0.5%

(Mertucci & Pacak, 2014)

Clinical Manifestations

V.L. Mertucci, K. Pacak / Cure Probl Cancer 38 (2014) 7–41

Table 2
Frequency of signs and symptoms in patients with PHEO/PGL.

Signs		Symptoms	
Hypertension	++++	Headaches	++++
Sustained hypertension	++	Palpitations	++++
Paroxysmal hypertension	++	Anxiety or nervousness	+++
Postural hypertension	+	Tremulousness	++
Tachycardia or reflex bradycardia	+++	Weakness and fatigue	++
Excessive sweating	++++	Nausea or vomiting	+
Pallor	++	Pain in chest or abdomen	+
Flushing	+	Dizziness or faintness	+
Weight loss	+	Paresthesias	+
Fasting hyperglycemia	++	Constipation (rarely diarrhea)	+
Decreased gastrointestinal motility	+	Visual disturbances	+
Increased respiratory rate	+		

Frequency: highest (++++) to lowest (+). Adapted with permission from Pacak.[105]

Clinical Manifestations

- HTN – 90% of pts
  - 40% paroxysmal HTN, which is a distinctive manifestation of PHEO
- NE secretion (mainly) by tumor
  - S/S reflect alpha activity over beta effects
  - **Hyperglycemia** d/t alpha inhibition of insulin & enhanced hepatic glucose output
  - ↑ metabolism = ↑O_2 consumption = hyperthermia
  - Vasoconstriction in extremities = pain, paresthesia, intermittent claudication, or ischemia
- Epi secretion by tumor
  - HTN & hypotension w/ syncope (alternating)
  - Epi surges → disproportionate β-adrenergic stimulated vasodilation while there is a contracted vascular space

Paroxysm

- Sudden & alarming HTN with
  - Severe throbbing HA, profuse sweating, palpitations, tachycardia, a sense of doom, anxiety, pallor, & nausea
  - Orthostatic hypotension
    - d/t plasma volume deficit or
    - Decrease tone in postural reflexes d/t sustained excess of catecholemines
  - S/S last several minutes to days → physical exhaustion
- Triggers
  - Pressure on tumor
  - Abd palpation, bowel movement
  - Mental or social stress does not initiate

ECG changes

- Common
  - ST, SVT, PVC
- May be seen
  - Non-specific ST & T wave changes
  - Prominent U waves
- Sometimes
  - R & L BBB
  - Ventricular strain
  - VT

Diagnostics

Diagnosis

- Biochemistry
  - Plasma metanephrine
  - Urine metanephrine
- Imaging studies
  - CT
  - MRI
  - Nuclear medicine

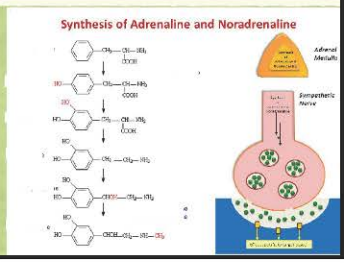
TABLE 33-10 Values for Catecholamines and Catecholamine Metabolites

Hormone/Metabolite	Normal Value
Vanillylmandelic acid, urine	2-7 mg/24 hr
Metanephrines, urine	Less than 1.3 mg/24 hr
Norepinephrine, urine	Less than 100 mcg/24 hr
Norepinephrine, plasma	150-450 pg/mL
Epinephrine, plasma	Less than 35 pg/mL
Catecholamines, free urinary	Less than 110 mcg/24 hr

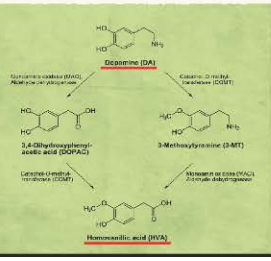
Biochemistry of Catecholamine

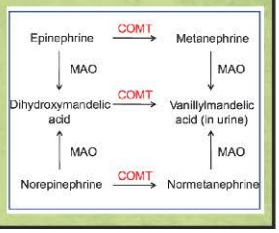
- Adrenal PHEO produces both Epi and Norepi
- Extraadrenal PGLs produce Norepi
- PHEO/PGL can produce dopamine sometimes, as well

Catecholamine Synthesis



Catecholamine Metabolism





Diagnosis

- Measurement of **plasma or urine metanephrines** is the **most accurate test** currently available (metabolism remains fairly constant) -- (4x > upper reference limit)
- Measurement of plasma or urine catecholamines is not always reliable due to fluctuating levels of catecholamine release. (4x > upper reference limit)
- Measurement of **methoxytyramine** can be valuable for detecting exclusively dopamine-secreting tumors and serve as a predictor of malignancy.
- If (+)for ↑Metanephrine or epinephrine, imaging can be focused on the adrenal gland or organ of Zuckerkandl.

Diagnosis

- **Chromogranin A (CgA),** a polypeptide commonly secreted by chromaffin cells: ↑ CgA is found in 91% of pts with PHEO/PGL but it is nonspecific marker of neuroendocrine tumors. When combined with catecholamine measurements, the sensitivity for PHEO/PGL DX can be close to 100%. (Martucci & Pacak, 2014)
- Chromogranin A has low sensitivity for diagnosis of PHEO and PGL, but it can be used as a marker for malignancy and as an easy marker of recurrence for follow-up.

False Positive Caution

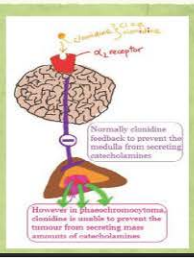
- Antidepressants (MAOI, Tricyclic, serotonin and NE reuptake inhibitors), some antihypertensives (β-blockers), and other common medications (Dopamine D2 receptor antagonists, sympathomimetics, chemotherapeutic agents, opiate analgesics, NMBA, Peptide and steroid hormones) can cause false positive elevations.
- Caffeine can ↑ catecholamine and metanephrine levels. It should be avoided before repeat testing.
- Caution with CKD pts, particularly on dialysis, can have ↑ plasma metanephrines even in the absence of PHEO/PGL.

False Positive caution

- Plasma catecholamine and metanephrine levels should be drawn through an indwelling catheter after pt has rested for at least 20 minutes in a dark, quiet room, to remove any environmental effects on stress levels.
- Pt should have fasted overnight before the blood draw.
- Use of age appropriate reference ranges is critical.
- Urine measurement should be done over 24-hour period.
- Interfering medications should be discontinued or avoided from at least 24 hrs before testing until testing is complete.

Clonidine Suppression test

- Can only be done for pts with ↑ Norepi or normetanephrine level.
- Most sensitive when performed with plasma normetanephrine level as the biomarker.
- Failure to suppress below the upper reference limit or by 40% of the initial value even after addition of the clonidine → should perform further workup for suspected PHEO/PGL.



Dx: Imaging Studies

- CT and MRI have similar sensitivity in detecting PHEO/PGL.
- Functional Imaging
  - 123I- or 131I-metaiodobenzylguanidine (MIBG)) Scintigraphy: can help detect primary or metastatic tumors missed on CT/MRI
    - MIBG has a structure that resembles NE and enters cell through NET (NE transporters).
    - 123I-MIBG is more sensitive and clinically useful
    - Limitations r/t false negative results in the cases of extra-adrenal tumors and tumors associated with SDHB mutations, and also miss metastatic dz
    - Suboptimal for HN-PGLs.
  - PET (Positron emission tomography)
    - FDA-PET, FDG-PET, FDOPA PET
  - Octreoscan
- SPECT (Single-photon emission CT)
- 68Ga-DOTA peptides
- US: limited application in general but valuable in evaluating liver mets or bladder tumors

Anesthesia for PGL & PHEO

Pre-operative

- Medical Management prior to excision goals:
  - Reverse effects of the excessive adrenergic stimulation
  - Pre-op antihypertensive therapy
  - Volume replacement
- Surgical Mortality Rate
  - 50%
  - 1% w/ pre-op management

A sudden surge of massive amounts of catecholamine can lead to a "storm". Without effective and timely interventions, complications like uncontrolled high blood pressure, spasm of the coronary arteries, irregular heart rhythms, weakened heart muscles, cerebral infarct, and pulmonary edema are inevitable, increasing the morbidity and mortality (M&M) rates

(Renard et al., 2011).

α-adrenergic antagonists

(Nagelhout & Plaus, 2014)

- **Phenoxybenzamine**
  - Halo alkylamine; α1 & α2 blockade
  - Noncompetitive & irreversible
  - Terminated by metabolism & generation of new α-receptors
  - S/E: orthostatic hypotension & nasal stuffiness
- Most Common PHEO pre-op rx
- DOA 24-48 hrs
- PO 60-250 mg/day (2-3 divided doses)
- 10-14 days to stabilize BP, restore IVC, & ↓ s/s
- Good alpha blockade shown if HCT ↓ by 5% during tx
- AM of surg → 1/2 to 1/3 of dose may be given

- Response of other drugs
  - Phenylephrine - ↓ response
  - NE – limited to β-agonist activity
  - "Epi - Reversal" – enhanced β2 response with a worsening hypotension & tachycardia

Catecholamine synthesis inhibitors

Phenoxybenzamine may be combined with:

Metyrosine (Demser):

- A competitive inhibitor of tyrosine hydroxylase, a critical enzyme in catecholamine synthesis
- Limited availability
- Cross BBB and deplete catecholamine→ S/E are depression, anxiety, sleepiness, requiring careful monitoring of pts

Alpha Receptors		Beta Receptors	
1. Vasoconstriction of a. Coronary arteries b. Veins 2. ↓motility of GIT smooth muscle cells			
α1 (postsynaptic)	**α2 (presynaptic)**	**β1 (postsynaptic)**	**β2 (postsynaptic)**
Gq protein coupled Activates **Phospholipase C** **PIP2 →IP3 + DAG**	**Gi protein** coupled Inhibits **Adenyl Cyclase** **ATP →X→cAMP**	**Gs protein** coupled Activates **Adenyl Cyclase** **ATP → cAMP**	
1. Vasoconstriction of blood vessels of a. Skin b. GIT c. Kidney d. Brain 2. Contraction of smooth muscles of a. Ureter b. Vas deferens c. Urethral sphincter d. Uterus e. Ciliary body (mydriasis) 3. Glucose metabolism a. Gluconeogenesis b. Glycolysis	1. Glucose metabolism a. Inhibits insulin release b. Stimulates glucagon release 2. Contraction of anal sphincter 3. Inhibits release of Norepinephrine	1. The heart a. ↑heart rate (+ chronotropic) b. ↑impulse conduction (+dromotropic) c. ↑contraction (+ inotropic) d. ↑ejection fraction 2. ↑renin release by Juxtaglomerular cells 3. ↑hunger a. ↑ghrelin release by stomach	1. Smooth muscle relaxation of a. Bronchus b. Bronchioles c. Detrusor muscle d. Uterine muscle 2. Contraction of urethral sphincter 3. ↑renin release by Juxtaglomerular cells 4. Glucose metabolism a. Inhibits insulin release b. Stimulate i. Gluconeogenesis ii. Glycolysis 5. Lipolysis 6. Thickened salivary secretion

α-receptor Antagonists

- **Phentolamine**
  - Imidazole, a competitive antagonist of α1- and α2-receptors.
  - Rapid onset after IV administration and a much shorter DOA compared to phenoxybenzamine.
  - Can be used for short-term control of HTN in pts with PHEO.
  - Recommended dose is 1-5 mg by slow IV push.
  - Also has been used for local infiltration of vasoconstricting agents.
  - 5-10 mg of phentolamine can be mixed with 10 ml NS and injected directly into the site of infiltration

(Nagelhout & Plaus, 2014)

α-receptor Antagonists

- Other selective α1-receptor antagonists (Lack of α2-blocking activity indicates no effect on NE levels.→ less tachycardia)
  - **Prazosin (Minipress)**
    - Used in the treatment of chronic HTN
    - Induces vasodilation in both arterioles and veins.
    - ↓Peripheral vascular resistance, CO, afterload.
    - Administered PO
    - SE: orthostatic hypotension
  - **Doxazosin (Cardura)**
  - **Terazosin (Hytrin)**

(Nagelhout & Plaus, 2014)

β-Blockers

A before B

- Beta blockers are to be initiated **only** after adequate α-blockade is achieved to prevent unhindered α stimulation (Jaffe, Schmieding, and Golianu, 2014)
- Used to control tachycardia, HTN, & catecholamine induced SVT
- Cardioselective β-blockers (metoprolol and atenolol) are frequently preferred over propranolol (nonselective β-blocker)
- Labetalol – not recommended as 1st line drug
  - d/t β > α - blocking → hypertensive crises
  - Labetalol can also interfere with MIBG uptake

Preop Anti-hypertensive Meds

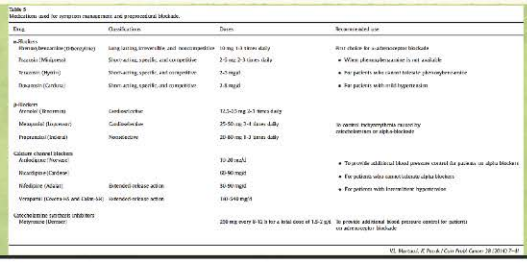


Table 5
Medications used for symptom management and preoperative blockade.

Drug	Classification	Doses	Recommended use
α-Blockers			
Phenoxybenzamine (Dibenzyline)	Long-acting, irreversible, and noncompetitive	10 mg, 1-3 times daily	First choice for α-adrenoceptor blockade
Doxazosin (Midapress)	Short-acting, specific, and competitive	2-8 mg; 2-3 times daily	• When phenoxybenzamine is not available
Terazosin (Hytrin)	Short-acting, specific, and competitive	2-5 mg qd	• For patients who cannot tolerate phenoxybenzamine
Prazosin (Cardura)	Short-acting, specific, and competitive	2-5 mg qd	• For patients with mild hypertension
β-Blockers			
Atenolol (Tenormin)	Cardioselective	12.5-25 mg; 2-3 times daily	
Metoprolol (Lopressor)	Cardioselective	25-50 mg; 2-4 times daily	In cardiac tachysymptomatic patients try catecholamines or alpha-blockade
Propranolol (Inderal)	Nonselective	20-40 mg; 2-3 times daily	
Calcium channel blockers			
Amlodipine (Norvasc)		10-20 mg/d	• To provide additional blood pressure control for patients on alpha blockers
Nicardipine (Cardene)		60-90 mg/d	• For patients who cannot tolerate alpha blockers
Nifedipine (Adalat)	Extended-release action	30-90 mg/d	• For patients with intermittent hypertension
Verapamil (Calan-SR and Calan-SR)	Extended-release action	180-540 mg/d	
Catecholamine synthesis inhibitors			
Metyrosine (Demser)		250 mg every 6-12 h for a total dose of 1.0-1 g/d	To provide additional blood pressure control for patients on alpha-receptor blockade

VL Marland, JE Peck / Curr Prob Cancer 39 (2015) 7–37

Other Pre-operative treatment

- Calcium channel blockers & Magnesium
  - As monotherapy – variable results
  - In conjunction w/ adrenergic blocking drugs
  - CCB: Amlodipine, Nicardipine, Nifedipine, Verapamil

Proposed end points:

1. No in-hospital BP > 160/90 24 hrs prior to surgery
2. No standing BP < 80/45
3. No ST-segment or T-wave abnormality not attributed to permanent defect
4. No marked symptoms of catecholamine excess; ≤ 1 PVC Q 5 min

(Nagelhout, 2014, p. 871)

Anesthetic Management

1. Choose drugs that do not stimulate catecholamine release

- **Precipitate** HTN in PHEO surgical pt
  - Indirect-acting amines
    - Ephedrine, methyldopa
  - Dopamine antagonist
    - Metoclopramide, droperidol
  - Blocking neuronal reuptake of catecholamine
    - Tricyclic antidepressants, cocaine
  - Histamine
    - Atracurium, Morphine
  - Contrast Dye
  - Glucagon
- Selective α2-receptor agonists
  - May be useful → reduce release of NE = ↓ BP & HR
  - Clonidine
  - Dexmedetomidine

Anesthetic Management

2. Monitoring technique to ID early catecholamine cardiovascular changes
   - Large bore IV
     - Tumors vascular
   - A-line
     - Monitoring & intervention
     - Regular assessment of
       - ABG
       - Electrolytes
       - Blood glucose levels
   - CVP
     - To manage fluids, inotropes, & vasoactive drugs

> Cardiac defibrillator and emergency vasoactive drugs should be readily available with the goal of heart rate less than 80 BPM and MAP of 80-100 mmHg (Renard et al., 2011)

Intra-operative

- Hyper vigilance during
  - Induction & intubation
  - Surgical manipulation of tumor
  - Ligation of tumor's venous drainage
    - ↓ BP d/t down regulation of receptors & abrupt ↓ in circulating catecholamine
    - Phenylephrine or Dopamine

Intra-operative

- Induction *(gentle)*
  - Barbiturates, Etomidate, or Propofol
  - Prior to DL & intubation
    - Mask with volatile anesthetic
    - Lidocaine 1-2 mg/kg 1 min prior
    - Short acting opioids
    - Rapid acting vasodilators readily available to tx HTN
      - Nitroprusside
- Volatile Anesthetic
  - Sevoflurane & short-acting opioids
    - cardiovascular stability & able to rapidly change anesthetic depth
  - Avoid Desflurane
    - Tachycardia & ↑ sympathetic stimulation
- Neuromuscular blockade
  - Succinylcholine
    - Fasciculation → press on tumor?
  - Goal
    - NDMB w/out vagolytic or histamine release
  - Avoid
    - Pancuronium – chronotropic effect
    - Atracurium – histamine release

Prepare Nitroprusside and phenylephrine drips in advance

Post-operative

- Tumor is excised, pt can experience profound ↓ BP d/t catecholamine depletion → admin sympathomimetic drugs and fluid resuscitation
- Phenylephrine may not be effective if residual α-blockade persists from the preoperative regimen → use **vasopressin**
- Perioperative **glucose monitoring** d/t significant fluctuations in blood sugar before and after the tumor removal
  - Classic symptoms of hypoglycemia masked by anesthetic agents & opioids
  - Undetected hypoglycemia → loss of consciousness & resp. arrest in severe cases

(Renard et al., 2011)

Post-operative

- Keep A-line in place
  - to assess BP & cardiac status
- 50% pts remain HTN during PACU
  - In spite of pheochromocytoma removal
- 75 % of pts return to normotension w/in 14 days post op
- Cause of post op HTN
  - Fluid shifts
  - Pain
  - Hypoxia
  - Hypercapnia
  - Autonomic instability
  - Urinary retention
  - Residual tumor
- Bilateral adrenalectomy
  - Steroid support may be necessary

Treating Crisis

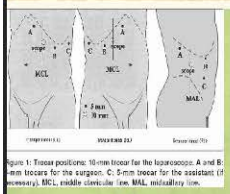
- Induction 200/130 mmHg → Remi gtt
- 225/160 → mass manipulation ntg gtt → nitroprusside
  - Propofol 200 + 200 mg& lasix 20 mg IV
  - Then sudden drop 90/60 w/ removal of mass→ ntg & nitroprusside stopped → Remi decreased and IVF given

Treatment Options

Surgery

- Medical management strategies for PHEO and PGL are "palliative option" at best. (Renard et al., 2011)
- Surgical resection remains the only curative treatment option for PHEO/PGL. (Martucci & Pacak, 2014)
- When the tumor size is too big, an open approach can be utilized via subcostal vs. vertical midline laparotomy, though subcostal approach is preferred.
- Extremely large tumor requires thoraco-phreno-laparotomy approach from the right side. (Renard et al., 2011)

Laparoscopic vs. Open Adrenalectomy



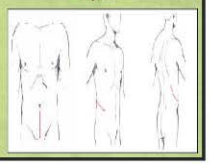
(Suzuki & Tsuru, 2005)

Laparoscopic:

Advantages
- Less postop pain
- Shorter length of stay
- Fewer complications
- More rapid convalescence than open approach

Disadvantages
- Anticipate catecholamine release with pneumoperitoneum
- The larger size of tumors are more challenging

Open



Surgical options

- For tumor size >6cm, laparoscopy still may be used but frequently converted to open procedure intraop
- For multiple, recurrent, or metastatic tumors, open procedures are more preferable
- Robotic assistance or robotic procedures can be used with similar success rates
- Full adrenalectomy to be performed in the absence of a genetic background, in pts with low risk for bil. Disease, or in pts with large tumors
- Cortex-sparing surgery may be sufficient if tumor is small for pts with bil. tumors or high risks for bil. tumors (i.e. VHL, MEN2 pts) in order to eliminate need for steroid replacement.

Other treatment options

- Radiofrequency ablation (RFA)
  - In some pts for whom surgery may not be the best option
  - For tumors in accessible locations
  - RFA successfully used on osseous and liver mets.
  - No serious adverse events reported.
  - Experienced radiologist and anesthesia provider should perform the technique to reduce risks for intraop catecholamine-induced HTN crises.

Other treatment options

Risk of malignancy for PGL is 20-30% vs. 10% malignancy risk for PHEO.
(Goers et al., 2011)

- External beam radiation (EBR)
  - For inoperable tumors or for symptom palliation
  - Particularly popular for treatment of bone lesions
  - Unclear outcome on metastatic lesions
  - Common treatment modality for nonresectable head and neck PGLs
    - Long-term local control rates with 5-, 10-, 15- year control rates were 96, 90, 90% respectively.
    - Glomus jugulare PGLs particularly popular candidates for EBR with high success rates and low toxicities.
  - Being replaced with radiosurgery using Gamma knife, LINAC, or Cyberknife for glomus jugulare tumors owing to more precise targeting of radiation and increased dose capability.

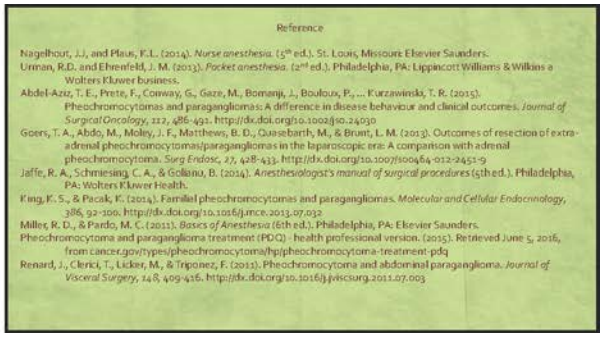
Other treatment options

- Radiotherapy
  - MIBG therapy for pts with (+) MIBG scintigraphy
    - It is critical to obtain recent MIBG scan to determine tumor uptake.
    - Pt to be taken off meds that can block MIBG uptake (Labetalol, TCA's, certain calcium antagonists)
    - Therapy is based on emission of β particles once the radioactive compound taken up into tumor cells.
    - Side effects: bone marrow aplasia, toxicity
    - Complete response is rare with highest reported rates only around 15%.
  - Therapies targeting somatostatin receptors under investigation more recently

Other treatment options

- Chemotherapy
  - For pts with metastatic disease to palliate pt symptoms, reduce or stop the rate of tumor growth, or shrink tumors.
  - Traditional chemo with **Cyclophosphamide, vincristine, and dacarbazine (CVD)** used most expensively with PHEO/PGL. Still remains one of the most effective treatment for widespread metastatic diseases.
  - CVD chemo well tolerated with relatively minor side effects (N/V, hair loss, thrombocytopenia, paresthesia)
  - If exhibiting toxicities, reduced doses or prolonged intervals between cycles can be offered.


Other treatment options
Molecular-targeted therapy
Sunitinib (sutent)
Originally developed for renal cell carcinoma treatment
Tyrosine kinase inhibitor, prevents angiogenesis through the targeting of vascular endothelial growth factor receptors and other angiogenic processes
Conflicting data


Reference
Nagelhout, J.J., and Plaus, K.L. (2014). Nurse anesthesia. (5th ed.). St. Louis, Missouri: Elsevier Saunders.
Urman, R.D. and Ehrenfeld, J. M. (2013). Pocket anesthesia. (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins a Wolters Kluwer business.
Abdel-Aziz, T. E., Prete, F., Conway, G., Gaze, M., Bomanji, J., Bouloux, P., ... Kurzawinski, T. R. (2015). Pheochromocytomas and paragangliomas: A difference in disease behaviour and clinical outcomes. Journal of Surgical Oncology, 112, 486-492. http://dx.doi.org/10.1002/jso.24030
Goers, T. A., Abdo, M., Moley, J. F., Matthews, B. D., Quasebarth, M., & Brunt, L. M. (2013). Outcomes of resection of extra-adrenal pheochromocytomas/paragangliomas in the laparoscopic era: A comparison with adrenal pheochromocytoma. Surg Endosc, 27, 428-433. http://dx.doi.org/10.1007/s00464-012-2451-9
Jaffe, R. A., Schmiesing, C. A., & Gollanu, B. (2014). Anesthesiologist's manual of surgical procedures (5th ed.). Philadelphia, PA: Wolters Kluwer Health.
King, K. S., & Pacak, K. (2014). Familial pheochromocytomas and paragangliomas. Molecular and Cellular Endocrinology, 386, 92-100. http://dx.doi.org/10.1016/j.mce.2013.07.032
Miller, R. D., & Pardo, M. C. (2011). Basics of Anesthesia (6th ed.). Philadelphia, PA: Elsevier Saunders.
Pheochromocytoma and paraganglioma treatment (PDQ) - health professional version. (2015). Retrieved June 5, 2016, from cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq
Renard, J., Clerici, T., Licker, M., & Triponez, F. (2011). Pheochromocytoma and abdominal paraganglioma. Journal of Visceral Surgery, 148, 409-416. http://dx.doi.org/10.1016/j.jviscsurg.2011.07.003

Appendix E
Poster Presentation

Anesthesia Care Implications of Paragangliomas and Pheochromocytomas

Adventist University of Health Sciences
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Project Mentor: Jessica Pena, CRNA, MSNA: JLR Medical Group
Project Chair: Steve Fowler, CRNA, DNP
Nurse Anesthesia Program, Adventist University of Health Sciences

Abstract

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare conditions that anesthesia providers may or may not encounter in their career. Due to the life-threatening and critical anesthetic implications in the perioperative period, the researchers deemed it prudent to present a lecture to the group of student registered nurse anesthetists (SRNAs) at Adventist University of Health Sciences. The educational lecture was provided with the goal of bridging the SRNAs' knowledge gaps regarding PHEO and PGL in general, and of helping them to be more familiar with PGL in particular.

Objectives

Educational presentation on PHEO and PGL:

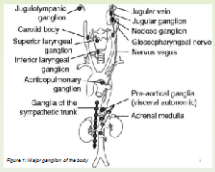
- Tell the similarities and the differences between Paraganglioma (PGL) and Pheochromocytoma (PHEO).
- Verbalize the anatomy and physiology of PGL and PHEO.
- Recognize the major genetic mutations associated with PGL and PHEO.
- Name the classic triad symptoms of PGL and PHEO.
- Tell the diagnostic tools for PGL and PHEO.
- Develop an anesthetic plan.

Methods

- Independent variable: PowerPoint Presentation
- When: Fall of 2016
- Subjects: 34 SRNAs in MSNA 501 and 504
- Dependent variable: pre- and post-test scores
- Measures: the difference between scores

Literature Review

Paraganglioma, umbrella term for rare tumors arising from the neural crest chromaffin tissues of the sympathetic and parasympathetic nervous systems. PGL are found anywhere along the ganglia, carotid body to the epididymis. A type of paraganglioma is PHEO, the term is designated exclusively for the tumors of the adrenal medulla. About 90% of PGLs are found in the abdomen and abdominal PHEO and PGL are usually catecholamine secreting.



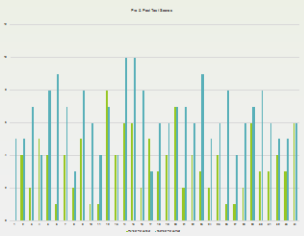
Current literature review revealed well-established data on PHEO in terms of pathophysiology, hereditary factors and connection to other gene mutations and neuroendocrine conditions, diagnostic tools, perioperative medical/anesthetic management, and surgical approaches. There are limited amounts of information on PGL due to rare incidences and lack of consistency in presentation. Functioning paragangliomas have similar management approaches to PHEO. Therefore, it is pertinent for anesthesia providers to be aware of potential life threatening hemodynamic instability when PGL is a diagnosis.

Results

For the purpose of analyzing the effectiveness of the PowerPoint lecture, the pre-test and post-test scores were compared. A paired t test revealed p value of < 0.05, affirming the statistical significance. The pre-test scores had shown the lack of knowledge in general, as evidenced by the low average test scores (3.47/11). The mean post-test scores (6.32/11) were definitely improved after the lecture, meeting the goal.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-Test	3.4706	34	1.94212	.33307
	Post-Test	6.3235	34	1.82736	.31340



Discussion

Scores were low in the pre-test, showing lack of knowledge. The convenience sample group was made up of both first year and second year nurse anesthesia students. There is a possibility that there were more first year students than second year students and most likely the first year students would not have been introduced to PHEO or PGL, causing lower scores. Furthermore, the post-test mean score (6.32/11) is low as well leading the researchers to believe the test might need to be reworded or better reflect the lecture.

Project Weaknesses

- Convenience sample
- Single site study
- Combined 1st and 2nd year SRNAs

Conclusion

The clinical implications are to present the education to nurse anesthesia students, so they may gain knowledge of PHEO and PGL. Allowing the student nurse anesthetist to be better prepared for the possibility of caring for a rare yet potentially life threatening event in the operating room. Since the education has shown statistical significance in increasing PHEO and PGL knowledge in those exposed, using this education will be helpful for current certified registered nurse anesthetists as a continuing education module or presentation.

References

1. References provided upon request