Pheochromocytomas and Paragangliomas

Subjects: Oncology

Contributor: Shams Y-Hassan , Henrik Falhammar

Pheochromocytomas and paragangliomas are rare catecholamine producing tumors. Early diagnosis is crucial to avoid life threatning complications. Surgical resection of the tumor is the only curative option. Preoperative management consists of alpha blockade and correction of intravascular volume.

pheochromocytoma paraganglioma adrenal tumor

Pheochromocytomas and paragangliomas (PPGLs) are rare neuro-endocrine tumors where the first arise from chromaffin tissues in the adrenal medulla and the second develop from chromaffin tissues in the extra-adrenal sympathetic and parasympathetic nervous system[1][2].

1. Introduction

In 1886, Dr. Felix Frankel described, on autopsy of a patient who collapsed suddenly and died, bilateral tumors of the adrenal gland[3]. Twenty-six years later in 1912, Dr. Ludwig Picks reported and coined the term pheochromocytoma[3].

PPGLs have an annual incidence of 3–8 cases per one million per year in the general population[4]. PPGLs synthesize, store, metabolize, and usually but not always secrete catecholamines (predominantly norepinephrine)[5]. The presentation of PPGLs may be vague and the interpretation of symptoms and signs may be difficult, which may explain the delay in the diagnosis in many cases[6]. PPGLs are more frequent in patients with adrenal incidentaloma with 0.6% to 4.2% being affected[7][8][9]. Currently, most PPGLs are diagnosed due to an incidentaloma, followed by the manifestation of catecholamine excess and finally because of screening in a previously known familial syndrome[2][6][10][11]. The clinical picture of PPGLs is depending on the type and amount of the catecholamine produced and grouped accordingly[5]. Norepinephrine-mediated alpha receptor stimulation results in vasoconstriction, volume contraction and hypertension; on the other hand, epinephrine beta 2 receptor stimulation results in skeletal muscle vasodilatation and hypotension[5]. PPGLs with predominantly dopamine-secreting tumors are rare. Association between dopamine hypersecretion and more aggressive malignant disease has been observed by some investigators[5][12]. The cardiovascular manifestations, including hypertension, associated with dopamine hypersecretion is not well-studied but in purely dopamine-producing tumors these are probably uncommon. The main features of PPGLs are paroxysmal palpitation, headache, sweating, pallor, tremors, and anxiety associated with paroxysmal or sustained hypertension[6][13]. Adrenal medullary hyperplasia is a precursor of pheochromocytoma, usually found due to screening of a familial syndrome, with milder symptoms and signs[14]. There are several familial syndromes (inherited tumor syndromes) with disease-causing mutations that are associated with PPGL (e.g., *RET*, *SDHx*, *VHL*, *NF1*, *MAX* and *TMEM127*)[2]. The biochemical phenotypes

associated with the different genetic causes of PPGL are slightly different. For example, *VHL*-associated pheochromocytomas are norepinephrine-secreting, whereas *SDHx* tumors may secrete dopamine and norepinephrine and *MEN2A*-related pheochromocytomas may secrete norepinephrine and epinephrine. Clinically, consideration of possible genetic causes for PPGLs determine the clinical management of such patients. For example, 123I-MIBG functional imaging is not useful in patients with *SDHx* mutations. Similarly, these patient groups require lifelong surveillance for both PPGLs and other related tumors.

2. PPGL Management

Early diagnosis of PPGL is crucial to avoid life-threatening complications. The initial investigation for suspected cases of PPGLs includes the measurement of plasma free metanephrines and/or urinary fractionated metanephrines[1]. Computed tomography scan and MRI are valuable for initial localization of the PPGLs tumors. Functional imaging with radiopharmaceutical agents as 123-I-MIBG scintigraphy or PET (e.g., Ga-DOTATOC) for confirmation and planning correct therapy.

Surgical resection of the tumor is the only curative option[1][15]. Preoperative management consists of alpha blockade and correction of intravascular volume[5][16]. The medical treatment before surgery is almost entirely based on expert opinion and observational studies. Treatment with alpha adrenergic receptor blocker is considered as the treatment of choice[15]. The two most commonly used drugs are phenoxybenzamine, which is a nonselective and noncompetitive alpha-1 and alpha-2 adrenergic receptor blocker. The second one is doxazosin, which is a selective and competitive alpha-1 adrenergic receptor blocker. It is recommended to initiate one of these two drugs 1-2 weeks before surgery with increasing dosages until the blood pressure targets are achieved. In a study comparing pretreatment with doxazosin and phenoxybenzamine during PPGL surgery, there was no difference in the duration of blood pressure outside the target range during resection of PPGL-tumor. However, phenoxybenzamine was more effective in preventing intraoperative systolic blood pressure above the target range and hemodynamic instability[17]. In an acute situation, PPGL-crisis alpha-blockers in the form of intravenous phentolamine is preferred over phenoxybenzamine because it has a rapid action. Calcium channel blockers (nifedipine or amlodipine) have also been used and preferably added to alpha adrenergic receptor blocker for further improvement of blood pressure control[15]. Beta- blockers are indicated to control tachycardia. Beta-blockers should not be initiated before alpha-blockers in the setting of PPGLs because of challenges in the cardiovascular management due to unopposed alpha blockade[5]. Beta- blockers in the form propranolol, metoprolol or atenolol can be used. Evidence to support the preference of beta-1 selective blockers over non-selective beta- blockers does not exist[1][15]. Labetalol with its more potent beta- than alpha-antagonist activities is not recommended as the initial therapy because it can lead to paradoxical hypertension and even hypertensive crisis[1].

Worth mentioning is that a multi-endocrine crisis may occur as thyrotoxicosis crisis together with pheochromocytoma multisystem crises have been reported[18] and this requires intensive cardiovascular management. In such cases, alpha- and beta-blockers may be started simultaneously. Such simultaneous treatment with alpha- and beta-blockers should be considered in PPGLs-induced left ventricular outlet tract

obstruction where treatment with beta-blockers is decisive. In preoperative assessment, it is mandatory to monitor heart rate, arterial blood pressure, and arrhythmias and to restore the blood volume to normal[19].

Careful follow-up to detect recurrence and prevent life-threatening complications is imperative. Different cardiovascular complications are treated accordingly. This has been discussed in detail elsewhere[5][20][21][22]. One very important point in the treatment of PPGL-induced cardiogenic shock is that inotropic medications are contraindicated[21][23][22]. Treatment with mechanical circulatory support as extracorporeal life support in cases of refractory hypotension is lifesaving[13][20].

References

1. Lenders, J.W.; Duh, Q.Y.; Eisenhofer, G.; Gimenez-Roqueplo, A.P.; Grebe, S.K.; Murad, M.H.; Naruse, M.; Pacak, K.; Young, W.F., Jr.; Endocrine, S. Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 2014, 99, 1915–1942.
2. Neumann, H.P.H.; Young, W.F., Jr.; Eng, C. Pheochromocytoma and Paraganglioma. N. Engl. J. Med. 2019, 381, 552–565.
3. Constantine A. Stratakis; Pheochromocytomas: Fabulous, Fascinating, and First (in everything)!. *Hormone and Metabolic Research* **2019**, *51*, 401-402, 10.1055/a-0957-9068.
4. Jenn Rachelle U. Santos; Alessandra Brofferio; Bruna Viana; Karel Pacak; Catecholamine-Induced Cardiomyopathy in Pheochromocytoma: How to Manage a Rare Complication in a Rare Disease?. *Hormone and Metabolic Research* **2018**, *51*, 458-469, 10.1055/a-0669-9556.
5. Joseph M. Pappachan; Nyo Nyo Tun; Ganesan Arunagirinathan; R Sodi; Fahmy W. F. Hanna; Pheochromocytomas and Hypertension. *Current Hypertension Reports* **2018**, *20*, 3, 10.1007/s11906-018-0804-z.
6. Henrik Falhammar; Magnus Kjellman; Jan Calissendorff; Initial clinical presentation and spectrum of pheochromocytoma: a study of 94 cases from a single center. *Endocrine Connections* **2018**, *7*, 186-192, 10.1530/ec-17-0321.
7. Yeomans, H.; Calissendorff, J.; Volpe, C.; Falhammar, H.; Mannheimer, B. Limited value of long-term biochemical follow-up in patients with adrenal incidentalomas-a retrospective cohort study. BMC Endocr. Disord. 2015, 15, 6.
8. Patrova, J.; Jarocka, I.; Wahrenberg, H.; Falhammar, H. Clinical Outcomes in Adrenal Incidentaloma: Experience from One Center. Endocr. Pract. Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol. 2015, 21, 870–877.
9. Mantero, F.; Terzolo, M.; Arnaldi, G.; Osella, G.; Masini, A.M.; Ali, A.; Giovagnetti, M.; Opocher, G.; Angeli, A. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the

Italian Society of Endocrinology. J. Clin. Endocrinol. Metab. 2000, 85, 637–644.

10. Amar, L.; Servais, A.; Gimenez-Roqueplo, A.P.; Zinzindohoue, F.; Chatellier, G.; Plouin, P.F. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J. Clin. Endocrinol. Metab. 2005, 90, 2110–2116.
11. Gruber, L.M.; Hartman, R.P.; Thompson, G.B.; McKenzie, T.J.; Lyden, M.L.; Dy, B.M.; Young, W.F.; Bancos, I. Pheochromocytoma Characteristics and Behavior Differ Depending on Method of Discovery. J. Clin. Endocrinol. Metab. 2019, 104, 1386–1393.
12. Oksana Hamidi; William F. Young; Nicole M. Iñiguez-Ariza; Nana Esi Kittah; Lucinda Gruber; Cristian Bancos; Shrikant Tamhane; Irina Bancos; Malignant Pheochromocytoma and Paraganglioma: 272 Patients Over 55 Years. *The Journal of Clinical Endocrinology & Metabolism* **2017**, *102*, 3296-3305, 10.1210/jc.2017-00992.
13. Shams Y-Hassan; Henrik Falhammar; Clinical features, complications, and outcomes of exogenous and endogenous catecholamine-triggered Takotsubo syndrome: A systematic review and meta-analysis of 156 published cases. *Clinical Cardiology* **2020**, *43*, 459-467, 10.1002/clc.23352.
14. Henrik Falhammar; Adam Stenman; Jan Calissendorff; Carl Christofer Juhlin; Presentation, Treatment, Histology, and Outcomes in Adrenal Medullary Hyperplasia Compared With Pheochromocytoma.. *Journal of the Endocrine Society* **2019**, *3*, 1518-1530, 10.1210/js.2019-00200.
15. Jacques W.M. Lenders; Michiel N. Kerstens; Laurence Amar; Aleksander Prejbisz; Mercedes Robledo; David Taieb; Karel Pacak; Joakim Crona; Tomáš Zelinka; Massimo Mannelli; et al.Timo DeutschbeinHenri J.L.M. TimmersFrederic CastinettiHenning DralleJřri WidimskýAnne-Paule Gimenez-RoqueploGraeme Eisenhofer Genetics, diagnosis, management and future directions of research of phaeochromocytoma and paraganglioma. *Journal of Hypertension* **2020**, *null*, null, 10.1097/hjh.0000000000002438.
16. Henrik Falhammar; Magnus Kjellman; Jan Calissendorff; Treatment and outcomes in pheochromocytomas and paragangliomas: a study of 110 cases from a single center. *Endocrine* **2018**, *62*, 566-575, 10.1007/s12020-018-1734-x.
17. Edward Buitenwerf; Thamara E Osinga; Henri J L M Timmers; Jacques W M Lenders; Richard A Feelders; Elisabeth M W Eekhoff; Harm R Haak; Eleonora P M Corssmit; Peter H L T Bisschop; Gerlof D Valk; et al.Ronald Groote VeldmanRobin P F DullaartThera P LinksMagiel F VoogdGötz J K G WietaschMichiel N KerstensPRESCRIPT-investigators Efficacy of α-Blockers on Hemodynamic Control during Pheochromocytoma Resection: A Randomized Controlled Trial. *The Journal of Clinical Endocrinology & Metabolism* **2019**, *105*, 2381-2391, 10.1210/clinem/dgz188.
18. Kodai Suzuki; Takahito Miyake; Hideshi Okada; Fuminori Yamaji; Yuichiro Kitagawa; Tetsuya Fukuta; Ryu Yasuda; Yoshihito Tanaka; Haruka Okamoto; Sho Nachi; et al.Tomoaki DoiTakahiro

YoshidaKeisuke KumadaShozo YoshidaHiroaki UshikoshiIzumi ToyodaShinji Ogura Thyrotoxic and pheochromocytoma multisystem crisis: a case report.. *Journal of Medical Case Reports* **2017**, *11*, 173, 10.1186/s13256-017-1299-y.

19. Kajetan Juszczak; Tomasz Drewa; Adrenergic crisis due to pheochromocytoma – practical aspects. A short review. *Central European Journal of Urology* **2014**, *67*, 153–155, 10.5173/ceju.2014.02.art7.
20. Y-Hassan, S.; Falhammar, H. Pheochromocytoma-and paraganglioma-triggered Takotsubo syndrome. Endocrine 2019, 65, 483–493.
21. Y-Hassan, S.; Tornvall, P. Epidemiology, pathogenesis, and management of takotsubo syndrome. Clin. Auton. Res. 2018, 28, 53–65.
22. Jelena-Rima Ghadri; Ilan Shor Wittstein; Abhiram Prasad; Scott Sharkey; Keigo Dote; Yoshihiro J. Akashi; Victoria Lucia Cammann; Filippo Crea; Leonarda Galiuto; Walter Desmet; et al.Tetsuro YoshidaRoberto ManfrediniIngo EitelMasami KosugeHolger M NefAbhishek DeshmukhAmir LermanEduardo BossoneRodolfo CitroTakashi UeyamaMenico CorradoSatoshi KurisuFrank RuschitzkaDavid WinchesterAlexander R LyonElmir OmerovicJeroen J BaxPatrick MeimounGuiseppe TarantiniCharanjit RihalShams Y.-HassanFederico MiglioreJohn D. HorowitzHiroaki ShimokawaThomas Felix LüscherChristian Templin International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *European Heart Journal* **2018**, *39*, 2047-2062, 10.1093/eurheartj/ehy077.
23. Jelena-Rima Ghadri; Ilan Shor Wittstein; Abhiram Prasad; Scott Sharkey; Keigo Dote; Yoshihiro J. Akashi; Victoria Lucia Cammann; Filippo Crea; Leonarda Galiuto; Walter Desmet; et al.Tetsuro YoshidaRoberto ManfrediniIngo EitelMasami KosugeHolger M NefAbhishek DeshmukhAmir LermanEduardo BossoneRodolfo CitroTakashi UeyamaMenico CorradoSatoshi KurisuFrank RuschitzkaDavid WinchesterAlexander R LyonElmir OmerovicJeroen J BaxPatrick MeimounGuiseppe TarantiniCharanjit RihalShams Y.-HassanFederico MiglioreJohn D. HorowitzHiroaki ShimokawaThomas Felix LüscherChristian Templin International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *European Heart Journal* **2018**, *39*, 2032-2046, 10.1093/eurheartj/ehy076.

Retrieved from https://encyclopedia.pub/entry/history/show/9002