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# CAUSES, RISK FACTORS, COMMON SYSPTOMS, ADDITIONAL SYMPTOMS, DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, TREATMENT AND PROGNOSIS OF PHOECHROMOCYTOMA

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ABSTRACT:-

Causes of phoechromocytoma are genetic mutations and sporadic cases. Risk factors for phoechromocytoma include family history, a very few genetic syndrome, multiple endocrine neoplasia type 2 (MEN 2), Con-Hippal vndau )VHL) syndrome, neuro fibramatous type 1 (NF 1), age, gender, stress, physical triggers and other mediacal conditions. Common symptoms are palpitations, perspiration, pain ( headache) and pressure ( high blood pressure).Additional symptoms include pallor and weight loss. Diagnosis is based on medical history, physical examination and names of laboratory tests are plasma or urinary metanephrines, plasma or urinary catechol amines and imaging studies such as CT scan ( Computed Topography), MRI scan (Magnetic Resonance Imaging), MIBG scxintigraphy and other functional tests are clonidine supressioin test, glucagon stimulation test. Differential diagnosis is dependent on anxiety and essential hypertension. Treatment is related to surgery, medication, pre operative preparation and regular follow up. The prognosis for phoechromocytoma is commonly favourable if diagnosed and treated in a promt manner. Finally it is concluded that phoechromocytoma is a rare adrenal gland tumor that can exhibit serious health consequences, if not diagnosed and treated in an prompt manner. Recognizing the symptoms and seeking medical treatment play a major role towards a favourable prognosis.

KEY WORDS: Tumor, adrenal medulla, hormone regulation, genetic mutations, sporadic cases, a very few genetic syndromes, multiple endocrine neoplasia type 2 (MEN 2), neuro fibramatosis type (NF 1), age. Gender,. other medical situations, palpations, perspiration, pain (headache) , pressure ( high blood pressure), panic (anxiety and panic attacks), pallor, weight loss, medical history, physical examination, plasma or urinary metanephrines, plasma or urinary cateocholamines, CT scan, MRI scan, , MIGB scintiography, clonidine suppression test , g;lucagon stimulation test, genetic screening hypothyroidism, hypoglycemia, drug

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

induced hypertension, neuro endocrine tumors, anemia, biopsy or surgical excision, surgery, pre operative preparation, regular follow up, genetic counselling, tumor size and life long hormone replacement therapy., .

***INTRODUCTION:-***

Pheochromocytoma is a rare, often benign tumor that originates in the adrenal glands. These tumors can lead to a range of symptoms due to the excess production of adrenaline and noradrenaline, two vital stress hormones. In this article, we will delve into the various aspects of pheochromocytoma, including its causes, symptoms, diagnosis, treatment options, and prognosis.

***WHAT IS PHOECHROMOCYTOMA:-***

Pheochromocytoma is a tumor that develops in the adrenal medulla, which is the inner part of the adrenal glands. These glands are situated on top of each kidney and play a crucial role in hormone regulation within the body. Pheochromocytomas are typically non-cancerous (benign), but they can lead to serious health complications.

***CAUSES AND RISK FACTORS:-***

**CAUSES OF PHOECHROMOCYTOMA:-**

*Genetic Mutations:* Pheochromocytoma can be caused by inherited genetic mutations, such as those in genes like RET, VHL, NF1, and SDHx, which increase the risk of tumor development.

*Sporadic Cases:* In many cases, pheochromocytoma occurs sporadically without a clear genetic cause.

**RISK FACTORS FOR PHOECHROMOCYTOMA:-**

*Family History:* A family history of pheochromocytoma or related genetic conditions increases the risk of developing the tumor.

*Certain Genetic Syndromes:*

Multiple Endocrine Neoplasia Type 2 (MEN2): Individuals with MEN2 are at a higher risk of developing pheochromocytoma.

Von Hippel-Lindau (VHL) Syndrome: VHL syndrome can predispose individuals to pheochromocytoma.

Neurofibromatosis Type 1 (NF1): NF1 is associated with an increased risk of pheochromocytoma.

*Age:* Pheochromocytoma can occur at any age but is most commonly diagnosed in adults between the ages of 30 and 50.

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

*Gender:* It affects both genders equally.

*Stress and Physical Triggers:* Stressful situations, trauma, or certain medical procedures can provoke symptoms in individuals with existing pheochromocytoma.

*Other Medical Conditions:* Conditions like paraganglioma (a related tumor), thyroid disorders, and certain hormone-producing tumors can be associated with pheochromocytoma.

*Certain Medications:* Some medications, such as certain antidepressants and stimulants, can trigger or exacerbate symptoms in individuals with pheochromocytoma.

***COMMON SYMPTOMS:-***

Pheochromocytoma is a rare tumor that develops in the adrenal glands, and it can lead to excessive production of catecholamines, such as adrenaline and noradrenaline. These hormones can cause a range of symptoms, often referred to as the “five P’s.”

*Palpitations:*

Rapid or irregular heartbeat.

Sensation of pounding in the chest.

*Perspiration:*

Profuse sweating, often without an apparent cause.

Sweating may be excessive, even in cool conditions.

*Pain (Headache):*

Severe headaches, often described as sudden and sharp.

Headaches may be recurrent and migrainous in nature.

*Pressure (High Blood Pressure):*

Markedly elevated blood pressure, sometimes reaching hypertensive crisis levels.

Blood pressure fluctuations, with episodes of extremely high readings.

*Panic (Anxiety and Panic Attacks):*

Episodes of intense anxiety or panic attacks.

Feelings of extreme nervousness, restlessness, or a sense of impending doom.

**ADDITIONAL SYMPTOMS:-**

*Pallor:*

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

Paleness of the skin.

May be noticeable during episodes of high blood pressure.

*Pallor:*

Abdominal pain or discomfort.

May be localized to the area overlying the adrenal glands.

*Weight Loss:*

Unexplained weight loss.

Due to increased metabolic rate associated with elevated catecholamines.

It's important to note that not everyone with pheochromocytoma will experience all of these symptoms, and the severity can vary. Some individuals may have intermittent or paroxysmal (sudden and severe) symptoms. If you suspect you have pheochromocytoma or are experiencing these symptoms, it's crucial to seek immediate medical attention, as this condition can be life-threatening if not properly managed.

***DIAGNOSIS:-***

Diagnosing pheochromocytoma can be challenging due to its rarity and the variability of symptoms. However, several tests and procedures are used to confirm its presence, including:

***Clinical Evaluation:***

*Medical History:* Gathering information about the patient's symptoms, family history, and any known genetic syndromes associated with pheochromocytoma (e.g., Multiple Endocrine Neoplasia Type 2).

*Physical Examination:* Checking for signs such as high blood pressure, palpitations, sweating, and abdominal tenderness.

**Laboratory Tests:**

*Plasma or Urinary Metanephrines:* Measuring metanephrines, which are breakdown products of catecholamines (epinephrine and norepinephrine), in blood or urine. Elevated levels may suggest pheochromocytoma.

*Plasma or Urinary Catecholamines:* Similar to metanephrines, measuring catecholamine levels can help in the diagnosis.

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

**Imaging Studies:**

*CT Scan (Computed Tomography):* A CT scan of the abdomen and pelvis is often the initial imaging test to visualize the tumor.

*MRI (Magnetic Resonance Imaging):* Sometimes used as an alternative to CT for imaging the adrenal glands and detecting pheochromocytomas.

*MIBG Scintigraphy:* This specialized nuclear medicine test can detect certain types of pheochromocytomas that may not be visible on CT or MRI.

**Functional Tests:**

*Clonidine Suppression Test:* Administering clonidine to assess the suppression of catecholamine release. A positive result suggests pheochromocytoma.

*Glucagon Stimulation Test:* Inducing catecholamine release with glucagon and measuring the response. Elevated catecholamine levels indicate pheochromocytoma.

**Genetic Testing:**

*Genetic Screening:* For patients with a family history of pheochromocytoma or certain genetic syndromes, genetic testing may be recommended to identify specific gene mutations (e.g., RET, VHL, SDHx) associated with the condition.

***DIFFERENTIAL DIAGNOSIS:-***

Pheochromocytoma symptoms can mimic other medical conditions, such as anxiety or essential hypertension. Differential diagnosis is crucial to exclude these possibilities.

*Essential Hypertension:* Pheochromocytoma can mimic high blood pressure, so ruling out essential hypertension is important.

*Anxiety or Panic Attacks:* The symptoms of pheochromocytoma, such as palpitations and anxiety, can overlap with anxiety or panic disorders.

*Hyperthyroidism:* Thyroid disorders can cause similar symptoms, like increased heart rate and sweating.

*Hypoglycemia:* Low blood sugar can lead to symptoms that resemble those of pheochromocytoma.

*Drug-induced Hypertension:* Certain medications, like stimulants or decongestants, can elevate blood pressure and cause similar symptoms.

*Other Adrenal Tumors:* Adrenal adenomas or carcinomas can present with similar symptoms.

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

*Neuroendocrine Tumors:* Tumors in other parts of the body, such as the lungs or gastrointestinal tract, can produce excessive catecholamines like pheochromocytomas.

*Anemia:* Severe anemia can lead to symptoms like fatigue and rapid heart rate.

Diagnosis often involves blood and urine tests to measure catecholamine levels, imaging studies like CT or MRI scans to locate the tumor, and confirmatory tests like the clonidine suppression test or the glucagon stimulation test. Consulting with a healthcare professional is crucial for an accurate diagnosis and appropriate treatment.

***Histopathology:***

*Biopsy or Surgical Excision:* If imaging and functional tests strongly suggest pheochromocytoma, a biopsy or surgical removal of the tumor is performed. Histopathological examination of the tissue confirms the diagnosis.

***Staging and Further Evaluation:***

*Staging Studies:* After diagnosis, additional tests, such as CT or MRI of the chest and bone scans, may be conducted to determine if the tumor has spread to other parts of the body.

It's important to note that the diagnosis of pheochromocytoma is complex and may require a multidisciplinary approach involving endocrinologists, radiologists, and surgeons. The specific diagnostic approach can vary depending on the patient's clinical presentation and medical history.

***TREATMENT OPTIONS:-***

*Surgery:* Surgical removal of the tumor is the primary treatment. This procedure is called adrenalectomy and can often be done laparoscopically.

*Medications:* Before surgery, or in cases where surgery is not immediately possible, medications like alpha-blockers (e.g., phenoxybenzamine) and beta-blockers (e.g., propranolol) may be prescribed to control blood pressure and manage symptoms.

*Preoperative Preparation:* Prior to surgery, patients may be given medications to stabilize blood pressure and reduce the risk of complications during surgery.

*Regular Follow-up:* After treatment, regular follow-up appointments are essential to monitor blood pressure and hormone levels, as pheochromocytoma can sometimes recur.

*Genetic Counseling:* Genetic testing and counseling may be recommended if there is a family history of pheochromocytoma, as some cases are hereditary.

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

***PROGNOSIS:-***

The prognosis for pheochromocytoma is generally favorable when diagnosed and treated promptly. Most pheochromocytomas are benign, and surgical removal can often cure the condition. However, if left untreated, the high blood pressure associated with pheochromocytoma can lead to serious complications, including stroke and heart attack.

*Early Detection and Diagnosis:*

Timely diagnosis and intervention significantly improve prognosis.

Delayed diagnosis can lead to complications and a poorer outcome.

*Surgical Treatment:*

Surgical removal of the pheochromocytoma is the primary treatment.

Complete tumor resection often results in a good prognosis.

*Location of the Tumor:*

The tumor's location within the adrenal gland or extra-adrenal sites can affect prognosis.

Adrenal tumors tend to have a better prognosis than extra-adrenal ones.

*Tumor Size:*

Smaller tumors generally have a better prognosis than larger ones.

Larger tumors may have a higher risk of malignancy.

*Malignancy:*

Malignant pheochromocytomas (pheochromocytoma that has spread) have a worse prognosis.

Early detection and treatment are crucial to prevent malignancy.

*Genetic Factors:*

Some hereditary syndromes are associated with pheochromocytomas (e.g., MEN2, VHL).

Prognosis may vary based on the underlying genetic mutation.

*Cardiovascular Complications:*

Pheochromocytoma can lead to severe hypertension and cardiovascular complications.

Proper blood pressure management is essential to prevent cardiac issues.

*Recurrence:*

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

Pheochromocytoma can recur, even after successful surgery.

Regular follow-up and monitoring are necessary to detect recurrences early.

*Adrenal Insufficiency:*

Surgical removal of the adrenal gland containing the tumor can lead to adrenal insufficiency.

Lifelong hormone replacement therapy may be required.

*Overall:*

With early diagnosis, appropriate treatment, and regular monitoring, many individuals with pheochromocytoma have a good prognosis.

Prognosis is generally better for benign, localized tumors compared to malignant or metastatic ones.

It's important to note that individual prognosis can vary widely based on specific circumstances and the patient's overall health. Consultation with a healthcare provider is essential for a personalized prognosis and treatment plan.

***Conclusion***

Pheochromocytoma is a rare adrenal gland tumor that can have serious health consequences if not diagnosed and treated promptly. Recognizing the symptoms and seeking medical attention is crucial for a favorable prognosis. With advancements in medical imaging and treatment techniques, the outlook for individuals with pheochromocytoma has improved significantly in recent years.

**REFERENCES OR FURTHER READING: -**

1. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF., Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42. [PubMed]
2. Plouin PF, Chatellier G, Fofol I, Corvol P. Tumor recurrence and hypertension persistence after successful pheochromocytoma operation. Hypertension. 1997 May;29(5):1133-9. [PubMed]
3. Neumann HP, Young WF, Krauss T, Bayley JP, Schiavi F, Opocher G, Boedeker CC, Tirosh A, Castinetti F, Ruf J, Beltsevich D, Walz M, Groeben HT, von Dobschuetz E, Gimm O, Wohllk N, Pfeifer M, Lourenço DM, Peczkowska M, Patocs A, Ngeow J, Makay Ö, Shah NS, Tischler A, Leijon H, Pennelli G, Villar Gómez de Las Heras K, Links TP, Bausch B, Eng C. 65 YEARS OF THE DOUBLE HELIX: Genetics informs precision practice in the diagnosis and management of pheochromocytoma. Endocr Relat Cancer. 2018 Aug;25(8):T201-T219. [PubMed]
4. Lo CY, Lam KY, Wat MS, Lam KS. Adrenal pheochromocytoma remains a frequently overlooked diagnosis. Am J Surg. 2000 Mar;179(3):212-5. [PubMed]
5. Ariton M, Juan CS, AvRuskin TW. Pheochromocytoma: clinical observations from a Brooklyn tertiary hospital. Endocr Pract. 2000 May-Jun;6(3):249-52. [PubMed]
6. Shen Y, Cheng L. Biochemical Diagnosis of Pheochromocytoma and Paraganglioma. In: Mariani-Costantini R, editor. Paraganglioma: A Multidisciplinary Approach [Internet]. Codon Publications; Brisbane (AU): Jul 02, 2019. [PubMed]

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

7. Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab. 2007 Nov;92(11):4069-79. [PubMed]
8. Gupta G, Pacak K., AACE Adrenal Scientific Committee. PRECISION MEDICINE: AN UPDATE ON GENOTYPE/BIOCHEMICAL PHENOTYPE RELATIONSHIPS IN PHEOCHROMOCYTOMA/PARAGANGLIOMA PATIENTS. Endocr Pract. 2017 Jun;23(6):690-704. [PMC free article] [PubMed]
9. Sundaresan PR, Banerjee SP. Differential regulation of beta-adrenergic receptor-coupled adenylate cyclase by thyroid hormones in rat liver and heart: possible role of corticosteroids. Horm Res. 1987;27(2):109-18. [PubMed]
10. Motulsky HJ, Insel PA. Adrenergic receptors in man: direct identification, physiologic regulation, and clinical alterations. N Engl J Med. 1982 Jul 01;307(1):18-29. [PubMed]
11. Ciaraldi TP, Marinetti GV. Hormone action at the membrane level. VIII. Adrenergic receptors in rat heart and adipocytes and their modulation by thyroxine. Biochim Biophys Acta. 1978 Jul 03;541(3):334-46. [PubMed]
12. Nazari MA, Rosenblum JS, Haigney MC, Rosing DR, Pacak K. Pathophysiology and Acute Management of Tachyarrhythmias in Pheochromocytoma: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jul 28;76(4):451-464. [PMC free article] [PubMed]
13. Kushnir A, Marks AR. The ryanodine receptor in cardiac physiology and disease. Adv Pharmacol. 2010;59:1-30. [PMC free article] [PubMed]
14. Wakabayashi T. Mechanism of the calcium-regulation of muscle contraction--in pursuit of its structural basis. Proc Jpn Acad Ser B Phys Biol Sci. 2015;91(7):321-50. [PMC free article] [PubMed]
15. Munakomi S, Rajbanshi S, Adhikary PS. Case Report: A giant but silent adrenal pheochromocytoma - a rare entity. F1000Res. 2016;5:290. [PMC free article] [PubMed]
16. Cajipe KM, Gonzalez G, Kaushik D. Giant cystic pheochromocytoma. BMJ Case Rep. 2017 Nov 08;2017 [PMC free article] [PubMed]
17. Lonser RR, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM, Oldfield EH. von Hippel-Lindau disease. Lancet. 2003 Jun 14;361(9374):2059-67. [PubMed]
18. Zbar B, Kishida T, Chen F, Schmidt L, Maher ER, Richards FM, Crossey PA, Webster AR, Affara NA, Ferguson-Smith MA, Brauch H, Glavac D, Neumann HP, Tisherman S, Mulvihill JJ, Gross DJ, Shuin T, Whaley J, Seizinger B, Kley N, Olschwang S, Boisson C, Richard S, Lips CH, Lerman M. Germline mutations in the Von Hippel-Lindau disease (VHL) gene in families from North America, Europe, and Japan. Hum Mutat. 1996;8(4):348-57. [PubMed]
19. Eisenhofer G, Walther MM, Huynh TT, Li ST, Bornstein SR, Vortmeyer A, Mannelli M, Goldstein DS, Linehan WM, Lenders JW, Pacak K. Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. J Clin Endocrinol Metab. 2001 May;86(5):1999-2008. [PubMed]
20. Frank-Raue K, Rondot S, Raue F. Molecular genetics and phenomics of RET mutations: Impact on prognosis of MTC. Mol Cell Endocrinol. 2010 Jun 30;322(1-2):2-7. [PubMed]
21. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. Nat Rev Dis Primers. 2017 Feb 23;3:17004. [PubMed]
22. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000 Mar;105(3 Pt 1):608-14. [PubMed]
23. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. von Recklinghausen's disease and pheochromocytomas. J Urol. 1999 Nov;162(5):1582-6. [PubMed]
24. Mannelli M, Lenders JW, Pacak K, Parenti G, Eisenhofer G. Subclinical phaeochromocytoma. Best Pract Res Clin Endocrinol Metab. 2012 Aug;26(4):507-15. [PMC free article] [PubMed]
25. Kuhweide R, Lanser MJ, Fisch U. Catecholamine-secreting paragangliomas at the skull base. Skull Base Surg. 1996;6(1):35-45. [PMC free article] [PubMed]
26. van Duinen N, Steenvoorden D, Kema IP, Jansen JC, Vriends AH, Bayley JP, Smit JW, Romijn JA, Corssmit EP. Increased urinary excretion of 3-methoxytyramine in patients with head and neck paragangliomas. J Clin Endocrinol Metab. 2010 Jan;95(1):209-14. [PubMed]

ISSN- 2394-5125 VOL 10, ISSUE 07, 2023

27. Pellitteri PK, Rinaldo A, Myssiorek D, Gary Jackson C, Bradley PJ, Devaney KO, Shaha AR, Netterville JL, Manni JJ, Ferlito A. Paragangliomas of the head and neck. Oral Oncol. 2004 Jul;40(6):563-75. [PubMed]
28. Papaspyrou K, Mewes T, Rossmann H, Fottner C, Schneider-Raetzke B, Bartsch O, Schreckenberger M, Lackner KJ, Amedee RG, Mann WJ. Head and neck paragangliomas: Report of 175 patients (1989-2010). Head Neck. 2012 May;34(5):632-7. [PubMed]
29. Timmers HJ, Kozupa A, Eisenhofer G, Raygada M, Adams KT, Solis D, Lenders JW, Pacak K. Clinical presentations, biochemical phenotypes, and genotype-phenotype correlations in patients with succinate dehydrogenase subunit B-associated pheochromocytomas and paragangliomas. J Clin Endocrinol Metab. 2007 Mar;92(3):779-86. [PubMed]
30. Tsujimoto G, Manger WM, Hoffman BB. Desensitization of beta-adrenergic receptors by pheochromocytoma. Endocrinology. 1984 Apr;114(4):1272-8. [PubMed]
31. Streeten DH, Anderson GH. Mechanisms of orthostatic hypotension and tachycardia in patients with pheochromocytoma. Am J Hypertens. 1996 Aug;9(8):760-9. [PubMed]
32. Song G, Joe BN, Yeh BM, Meng MV, Westphalen AC, Coakley FV. Risk of catecholamine crisis in patients undergoing resection of unsuspected pheochromocytoma. Int Braz J Urol. 2011 Jan-Feb;37(1):35-40;discussion 40-1. [PubMed]