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THURSDAY 10TH NOVEMBER 5PM WAT

ABIOLA ODUWOLE IS INVITING YOU TO A SCHEDULED ZOOM MEETING.

ASPAE WEBINAR: PHAECHROMOCYTOMA IN CHILDREN

Meeting ID: 884 1312 8660
Passcode: 795335

OUR AWESOME SPEAKERS:

PROF ABIOLA ODUWOLE
Introduction and Moderator

DR ELIZABETH OYENUSI
Pathophysiology, Clinical Features and Management

DR IJEOMA OHUCHE
Case presentations

Phaechromocytoma/Paraganglioma in Children

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OUTLINE

- Introduction
- Epidemiology
- Pathophysiology
- Clinical Features
- Management
- Complications
- Conclusion

INTRODUCTION

- Pheochromocytoma (PCC) and paraganglioma (PGL) [PPGL] are rare neoplasms, which arise from chromaffin cells.
- Tumors : adrenal gland :PCC (80-85%)
- Extra-adrenal locations: PGL: (15-20%)

- Exceptionally rare neoplasm in children: 0.2-0.5 cases/million

(Park 2021, Bholah 2017)

EPIDEMIOLOGY

- Most common endocrine tumour in children
- Childhood PCC/PGL : 9.6-20% of all cases
- 0.5-1% of pediatric hypertension
- Most studies report slight male preponderance

- PCC/PGL often occur as sporadic tumors, but sometimes, part of Hereditary Tumour Syndromes (HTS) :

- Von Hippel Lindau (VHL) disease (20%)

-(MEN) 2A and 2B, the familial PGL syndromes (PGL1–5: mutations in succinate dehydrogenase (SDH) subunits)

- more rarely: (NF) type 1, MEN1 and the tuberous sclerosis complex.

(Park- 2021, Pereira-2018, Mishra-2014, Waguespack -2010)

EPIDEMIOLOGY

- The “rule of 10” –death of an axiom *(Dluhy-2002, Neumann -2002)*
- Formerly used to describe PCC/PGLs is as follows: 10% are extra-adrenal, and of those, 10% are extra-abdominal; 10% are malignant; 10% are found in children; 10% of patients are normotensive; and 10% are hereditary.

- 21st century, 10% rule was dashed by a study from Neumann *et al*, which reported germline mutation in 24% of apparently sporadic PCC/PGL patients.
- Currently, 50-70% of pediatric PCC/PGL cases are associated with germline mutations (*Park- 2021)*

- Higher % of extra-renal tumours, more children with hypertension

(Sarathi -2017, Tripathy -2017)

Country	Authors/ Year	Study Period(y)	No of Cases	M/F	Age(y)	PCC/PGL	Treatment	Mortality
Sudan	Elaraki 2021	5	8	3:1	6-17	8/0	Adrenalectomy(7)	None
S Africa	Huddle 2011	30	54	1:3.2	8-57	34/20	Surgery (53)	4
S Africa	Zorgani 2018	14	35	1:1.5	11-69	24/10/1	Surgery (34)	2
France	Tersant 2020	16	81	1.5:1	2.2-18	41/40	Surgery (78)	2
Turkey	Eren 2015	7	5	1:4	9.6-16	5/0	Adrenalectomy	None
Korea	Park 2021	25	23	2.5:1	6.8-20.8	14/9	Surgery	None

PATHOPHYSIOLOGY

- Distinction between the types of hormones secreted by adrenal or extra-adrenal tumours comes from PNMT
- PNMT is in the adrenal gland, with its expression dependent upon onsite cortisol.
- Adrenal gland tumours : secrete epinephrine and norepinephrine
- Extra-adrenal tumors secrete norepinephrine and dopamine
- VHL & Familial PGL syndromes: mainly noradrenergic
- MEN2 &NF1 : mainly adrenergic

(Bholah- 2017, Waguespack-2010)

CLINICAL FEATURES

- Significant hypertension with

- the classic triad of palpitations, diaphoresis and headaches.

- Syncope
- Tremor
- Anxiety
- Weight loss
- Behavioural changes
- Decline in school performance
- Non specific: diarrhoea, low-grade fever

(Elaraki-2021, Ohuche -2020, Bholah- 2017, Waguespack-2010)

CLINICAL FEATURES

- Complications of catecholamine excess

-hypertensive crisis (stroke, seizures, etc)

-cardiomyopathy

-Hypertensive retinopathy

-pancreatitis

-multiorgan failure and death

- Non-secretory tumours:mass effect
- Haematuria and obstructive uropathy (bladder PGLs)
- Asymptomatic: screening or investigation of an abdominal mass

(Elaraki-2021, Bholah- 2017, Tripathy-2017,Waguespack-2010)

INVESTIGATIONS: SERUM

- ✓Detection and quantification of catecholamines and their metabolites in blood and urine.
- ✓ The diagnostic test of choice presently is the measurement of fractionated plasma and /or urine metanephrines and normetanephrines
- ✓whose sensitivities are approaching a 100% (more than 4-fold elevation highly suggestive).
- ✓Vanillylmandelic acid (VMA) may be useful if above not available
- ✓Suspicion of dopamine-secreting : Homovanillic Acid

(Lenders -2014,2017,Waguespack-2010, Erdelyi-2011)

INVESTIGATIONS: IMAGING

- CT scanning is the preferred imaging modality because of its outstanding spatial resolution, is superior to MRI.
- MRI is reserved for

-metastatic disease,

-intracardiac or skull base and neck paragangliomas,

-postoperative surgical clips,

-allergy to CT contrast,

-and when radiation exposure should be limited: children, pregnant women, and patients with known germline mutations.

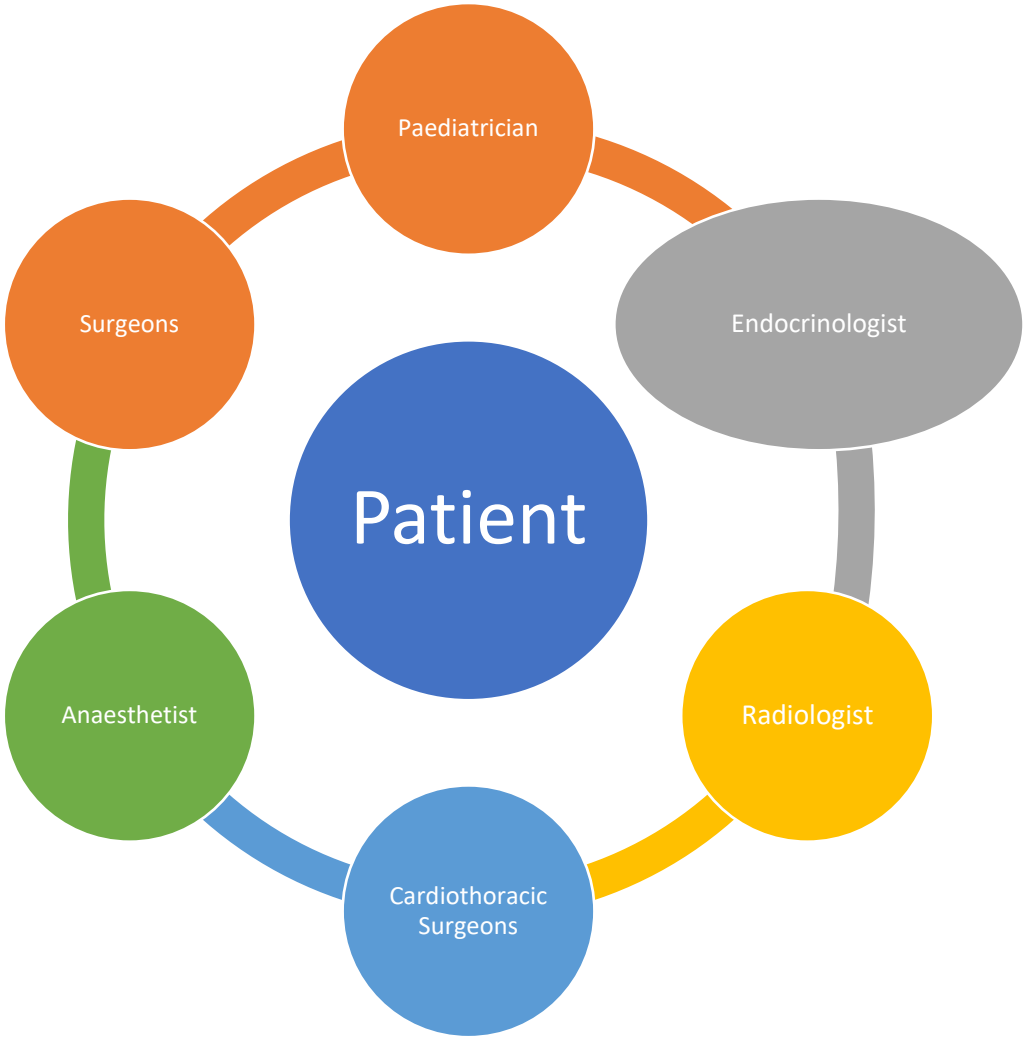
(Lenders -2014,2017,Waguespack-2010)

INVESTIGATIONS: IMAGING

- Functional imaging: provides a substantially higher specificity than anatomical imaging : multi-focal or metastatic disease.
- Specific ligands targeting either specific cell membrane transporters or vesicular catecholamine transport systems are available.
- Iodine123-metaiodobenzylguanidine (123I-MIBG) : sensitivity for detection of PCC is excellent (nearly 100%), but is unacceptably low for PGL (56% to 75%)-and metastases, particularly when associated with underlying succinate dehydrogenase (SDHx) mutations
- 111In-pentetreotide, 18F-fluorodeoxyglucose (18F-FDG), 18F-fluorodihydroxyphenylalanine (18F-FDOPA) and 68Ga-labeled DOTA(0)-Tyr(3)-octreotide (68Ga-DOTATATE)
- The clinical impact of functional imaging in all PCC/PGL patients remains undefended.

(Lenders -2014,2017,Waguespack-2010)

MANAGEMENT : MULTIDISCIPLINARY TEAM



TREATMENT: PREOPERATIVE PREPARATION

Mainstay is Surgery, but preop medical prep important.

- Initiated for 1–2 wk before surgery
- α_1-adrenergic blockade is usually the therapy of choice, and the primary agent used in children is the noncompetitive α_1 blocker Phenoxybenzamine (long acting).
- Selective $\alpha_1$blockers such as prazosin and doxazosin, Ca channel blockers nifedipine, nicardipine can also be used
- Symptomatic postural hypotension may occur, so titrate doses at the beginning

(Ramachandran-2017, Lenders -2014,2017, Waguespack-2010, Pacak-2007)

TREATMENT: PREOPERATIVE PREPARATION

- β-blocking agent (*e.g.* atenolol [preferred] propranolol or metoprolol) added next(after 2 days) to control reflex tachycardia.
- A β-blocker should never be used as a single agent
- Metyrosine is a competitive inhibitor of tyrosine hydroxylase (controversial)
- Few days before surgical intervention, oral salt loading
- Some centres routinely admit patients for IV fluids to reverse catecholamine-induced blood volume contraction.

(Ramachandran-2017, Lenders -2014,2017, Waguespack-2010, Pacak-2007)

TREATMENT : SURGERY

- Exploratory Laparatomy and tumour excision
- Laparoscopic adrenalectomy for pheochromocytomas.

- To circumvent the morbidity of bilateral adrenalectomy, cortical sparing adrenalectomy is being offered to the patients with bilateral PCC.

-Cortical-sparing procedures should be considered for the adrenal with the least tumor bulk

-Attractive in young children and children at risk for non-compliance with the lifelong glucocorticoid & mineralocorticoid replacement required after bilateral adrenalectomy.

-However, there is a risk for recurrent PCC in the remnant.

(Rao-2016, Lenders -2014,2017, Mishra-2014, Waguespack -2010)

TREATMENT : INTRA-OPERATIVE CARE

- Hemodynamic instability: hypertension before tumor removal and hypotension after tumor isolation.
- Management of hypertension: with short acting and potent vasodilators.
- Sodium nitroprusside and nitroglycerine: commonly used for intraoperative control of hypertension.
- Esmolol (short-acting β1 antagonist) OR Labetalol (α and β receptors antagonist) - useful parenteral adjunct to vasodilators
- Bleeding may occur especially with tumours near the great vessels (blood must be available)

(Ramachandran-2017, Lenders 2017, Waguespack-2010)

TREATMENT : POST-OPERATIVE CARE

- Usually require an ICU or high dependency unit admission.
- Withdrawal of catecholamine effect will result in hypotension (20–70%)

-dependent on nature of preoperative alpha-antagonist and intraoperative hypotensive agents

- Fluid loading along with vasopressor infusion is required to counteract the hypotension, usually required for a short duration

- refractory hypotension and prolonged vasopressor use have been reported

- Severe hypoglycemia, post op can occur.

-Hourly blood sugar monitoring, at least for the initial 12–24 h of the postoperative period, is mandatory.

(Elaraki-2021, Lenders 2017, Waguespack-2010)

FOLLOW-UP

- Genetic testing (pre and post op depends on availability) : esp PGL and metastatic disease –should undergo testing of succinate dehydrogenase (SDH) mutations
- Risk of metastases or local recurrence -5% in a 5year follow-up period
- Follow-up should be lifelong in patients with an increased risk for recurrence: in young patients (<20years of age), patients who had gland-sparing procedures for multicentric tumours, syndromes, large tumours)
- Includes:

- Medical History
- BP measurement including essential examination

-biochemical testing

-imaging MRI (esp SDHx gene mutations because routine biochemical screening may fail to detect these tumours)

(Lenders- 2014, 2017, Waguespack-2010)

COMPLICATIONS OF PCC/PGL

- Long standing hypertension

-Congestive cardiac failure

-Hypertensive retinpathy

-Hypertensive encephalopathy

-Pulmonary oedema

- Cathecholamine induced cardiomyopathy
- Renal failure
- Hyperglycaemic crisis

CONCLUSION/TAKE HOME MESSAGES

- Hypertension in children is mostly secondary.
- BP measurement in paediatrics is essential.
- PCC/PGL are rare but high index of suspicion should be maintained.
- Early diagnosis and intervention are important.
- Management involves a multidisciplinary team for optimal outcomes.
- Follow up of patients is crucial because of recurrence.
- Routine genetic screening of these children is useful for the detection and timely management of familial PCC.

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Thank You