Aminas Biogénicas- Abordagem clínica dos tumores produtores de catecolaminas

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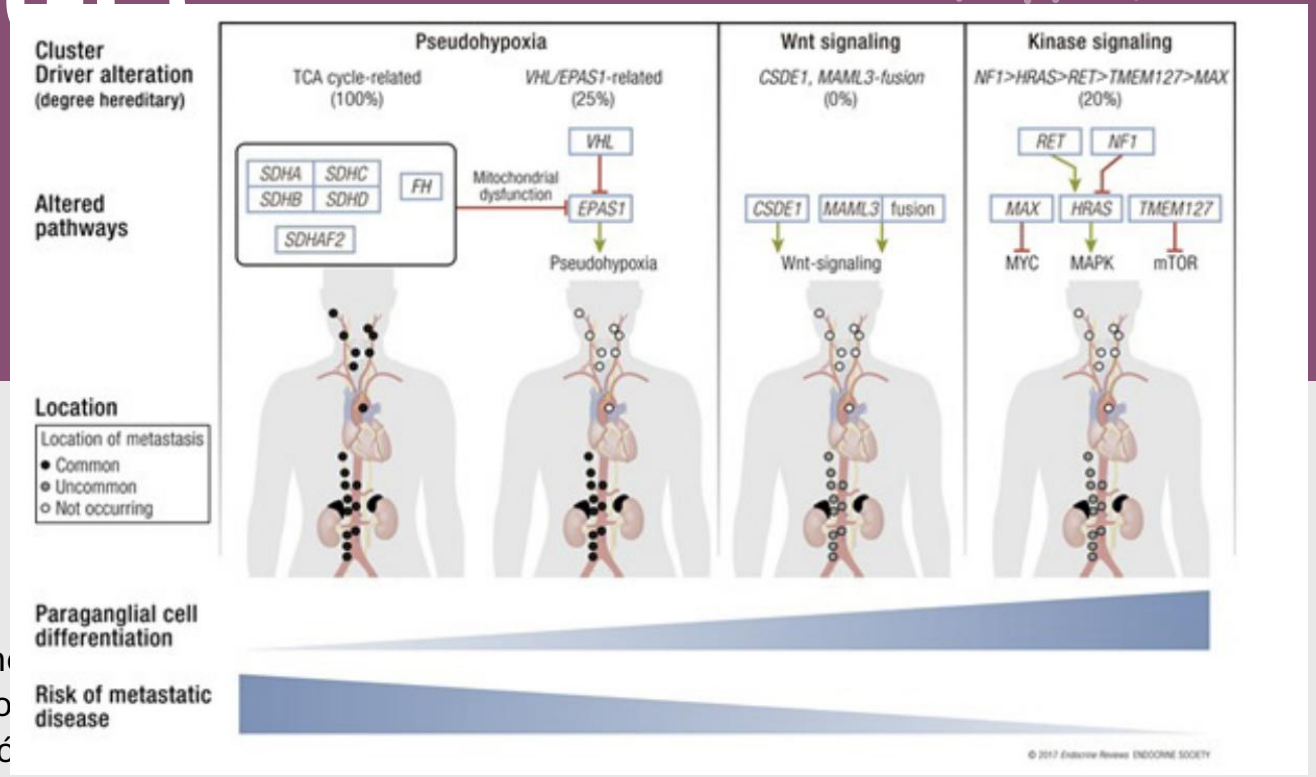
Agenda

1. Introdução
2. Casos Clínicos
    1. Doseamento de catecolaminas
    2. Interferências farmacológicas
    3. Interferências patológicas
    4. População idosa
3. Mensagens Finais

Introdução

Feocromocitomas e paragangliomas (FEO/PGL)



Tumores neuroendócrin
derivados de células cro
do sistema nervoso autó
Capacidade de sintetizar, metabolizar e secretar catecolaminas.

grande variabilidade clínica

catecolaminas em metanefrina, normetanefrina e 3-metoxitiramina, independentemente da libertação para a circulação

Grupo tumoral biologicamente heterogéneo > até 30–40% associados a mutações germinativas (agrupamento em diferentes clusters, com correlação com fenótipo bioquímico e clínico)

Tischler AS, deKrijger RR. 15 YEARS OF PARAGANGLIOMA: Pathology of pheochromocytoma and paraganglioma. Endocr Relat Cancer. 2015 Aug;22(4):T123-33. doi: 10.1530/ERC-15-0261.

Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline

Jacques W. M. Lenders, Quan-Yang Duh, Graeme Eisenhofer, Anne-Paule Gimenez-Roqueplo, Stefan K. G. Grebe, Mohammad Hassan Murad, Mitsuhide Naruse, Karel Pacak, and William F. Young, Jr

Radboud University Medical Center (J.W.M.L.), 6500 HB Nijmegen, The Netherlands; VA Medical Center and University of California, San Francisco (Q.-Y.D.), San Francisco, California 94121; University Hospital Dresden (G.E.), 01307 Dresden, Germany; Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Génétique, (A.-P.G.-R.), F-75015 Paris, France; Université Paris Descartes (A.-P.G.-R.), F-75006 Paris, France; Mayo Clinic (S.K.G.G., M.H.M.), Rochester, Minnesota 55905; National Hospital Organisation Kyoto Medical Center (M.N.), Kyoto 612-8555; Japan; *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (K.P.), Bethesda, Maryland 20892; and Mayo Clinic (W.F.Y.), Rochester, Minnesota 55905

Objective: The aim was to formulate clinical practice guidelines for pheochromocytoma and paraganglioma (PPGL).

Participants: The Task Force included a chair selected by the Endocrine Society Clinical Guidelines Subcommittee (CGS), seven experts in the field, and a methodologist. The authors received no corporate funding or remuneration.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence. The Task Force reviewed primary evidence and commissioned two additional systematic reviews.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, European Society of Endocrinology, and Americal Association for Clinical Chemistry reviewed drafts of the guidelines.

Conclusions: The Task Force recommends that initial biochemical testing for PPGLs should include measurements of plasma free or urinary fractionated metanephrines. Consideration should be given to preanalytical factors leading to false-positive or false-negative results. All positive results require follow-up. Computed tomography is suggested for initial imaging, but magnetic resonance is a better option in patients with metastatic disease or when radiation exposure must be limited. ^{123}I-metaiodobenzylguanidine scintigraphy is a useful imaging modality for metastatic PPGLs. We recommend consideration of genetic testing in all patients, with testing by accredited laboratories. Patients with paraganglioma should be tested for *SDHx* mutations, and those with metastatic disease for *SDHB* mutations. All patients with functional PPGLs should undergo preoperative blockade to prevent perioperative complications. Preparation should include a high-sodium diet and fluid intake to prevent postoperative hypotension. We recommend minimally invasive adrenalectomy for most pheochromocytomas with open resection for most paragangliomas. Partial adrenalectomy is an option for selected patients. Lifelong follow-up is suggested to detect recurrent or metastatic disease. We suggest personalized management with evaluation and treatment by multidisciplinary teams with appropriate expertise to ensure favorable outcomes. (***J Clin Endocrinol Metab* 99: 1915–1942, 2014**)

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European Journal of Endocrinology, 2023, **189**, G1–G42
https://doi.org/10.1093/ejendo/lvad066
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Clinical Practice Guideline

European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors

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Abstract

Adrenal incidentalomas are adrenal masses detected on imaging performed for reasons other than suspected adrenal disease. In most cases, adrenal incidentalomas are nonfunctioning adrenocortical adenomas but may also require therapeutic intervention including that for adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma, or metastases. Here, we provide a revision of the first international, interdisciplinary guidelines on incidentalomas. We followed the Grading of Recommendations Assessment, Development and Evaluation system and updated systematic reviews on 4 predefined clinical questions crucial for the management of incidentalomas: (1) How to assess risk of malignancy?; (2) How to define and manage mild autonomous cortisol secretion?; (3) Who should have surgical treatment and how should it be performed?; and (4) What follow-up is indicated if the adrenal incidentaloma is not surgically removed?

Selected Recommendations: (1) Each adrenal mass requires dedicated adrenal imaging. Recent advances now allow discrimination between risk categories: Homogeneous lesions with Hounsfield unit (HU) ≤ 10 on unenhanced CT are benign and do not require any additional imaging independent of size. All other patients should be discussed in a multidisciplinary expert meeting, but only lesions >4 cm that are inhomogeneous or have HU >20 have sufficiently high risk of malignancy that surgery will be the usual management of choice. (2) Every patient needs a thorough clinical and endocrine work-up to exclude hormone excess including the measurement of plasma or urinary metanephrines and a 1-mg overnight dexamethasone suppression test (applying a cutoff value of serum cortisol ≤50 nmol/L [≤1.8 µg/dL]). Recent studies have provided evidence that most patients without clinical signs of overt Cushing's syndrome but serum cortisol levels post dexamethasone >50 nmol/L (>1.8 µg/dL) harbor increased risk of morbidity and mortality. For this condition, we propose the term "mild autonomous cortisol secretion" (MACS). (3) All patients with MACS should be screened for potential cortisol-related comorbidities that are potentially attributably to cortisol (eg, hypertension and type 2 diabetes mellitus), to ensure these are appropriately treated. (4) In patients with MACS who also have relevant comorbidities surgical treatment should be considered in an individualized approach. (5) The appropriateness of surgical intervention should be guided by the likelihood of malignancy, the presence and degree of hormone excess, age, general health, and patient preference. We provide guidance on which surgical approach should be considered for adrenal masses with radiological findings suspicious of malignancy. (6) Surgery is not usually indicated in patients with an asymptomatic, nonfunctioning unilateral adrenal mass and obvious benign features on imaging studies. Furthermore, we offer recommendations for the follow-up of nonoperated patients, management of patients with bilateral incidentalomas, for patients with extra-adrenal malignancy and adrenal masses, and for young and elderly patients with adrenal incidentalomas. Finally, we suggest 10 important research questions for the future.

Keywords: adrenal tumors, diagnostic workup, therapy, follow-up

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Lenders JW, et alJr; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42. doi: 10.1210/jc.2014-1498. Erratum in: J Clin Endocrinol Metab. 2023 Apr 13;108(5):e200. doi: 10.1210/clinem/dgad064

Fassnacht M, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2023 Jul 20;189(1):G1-G42. doi: 10.1093/ejendo/lvad066.

1.0 Biochemica
Pheochromocy

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Table 1. Pharmacological causes of method-specific analytical interferences for catecholamines or for normetanephrine, metanephrine and methoxytyramine in urine (U) or plasma (P)

	Change in results for catecholamines		Change in results for metanephrines or methoxytyramine	
HPLC-ECD /FD				
Labetalol	E (U, P)	↑↑↑	NMN & MN (U, P)	↑↑↑
Sotalol			(U, P)	↑↑↑
Buspirone			MN (U)	↑↑↑
Acetaminophen	NE & E (U)	↑↑↑	NMN (U, P)	↑↑↑
Methyldopa[a]	E & DA (U)	↑↑↑		
Amoxicilline			NMN (U)	↑↑↑
Rifampicine	NE (U)	↑↑↑		
Sulfasalzine[b]			NMN (U)	↑↑↑
MHBA[c]			NMN, MN, MTY (U)	↓↓↓
Methenamine			NMN & MN (U)	↑↑↑
LC-MS/MS				
HMMA*			NMN (P)	↑↑↑
Midodrine**			MN (P)	↑↑↑

Abbreviations: DA, dopamine; E, epinephrine; HMMA, 4-hydroxy-3-methoxymethamphetamine; HPLC, high pressure chromatography with electrochemical detection; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MHBA, 3-methoxy-4-hydroxybenzylamine; MN, metanephrine; NE, norepinephrine; NMN, normetanephrine; MTY, methoxytyramine.
*As metabolite of 3,4 methylenedioxymethamphetamine (MDMA, Ecstasy)
**The midodrine metabolite desglymidodrine
[a]Due to the metabolite alpha-methylnorepinephrine
[b]And its prodrug mesalamine
[c]A constituent of curry leaves.

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Deutschbein T, et al. Influence of various confounding variables and storage conditions on metanephrine and normetanephrine levels in plasma. Clin Endocrinol (Oxf). 2010 Aug;73(2):153-60. doi: 10.1111/j.1365-2265.2009.03761.x. Epub 2009 Dec 18.
Pommer G, et al. Preanalytical Considerations and Outpatient Versus Inpatient Tests of Plasma Metanephrines to Diagnose Pheochromocytoma. J Clin Endocrinol Metab. 2022 Aug 18;107(9):e3689-e3698. doi: 10.1210/clinem/dgac390
de Jong WH, et al. Dietary influences on plasma and urinary metanephrines: implications for diagnosis of catecholamine-producing tumors. J Clin Endocrinol Metab. 2009 Aug;94(8):2841-9. doi: 10.1210/jc.2009-0303. Epub 2009 Jun 30.

2.0 Imaging Studies

2.1 We recommend that imaging studies to locate PPGL should be initiated once there is clear biochemical evidence of a PPGL. (**1**|⊕⊕◯◯)

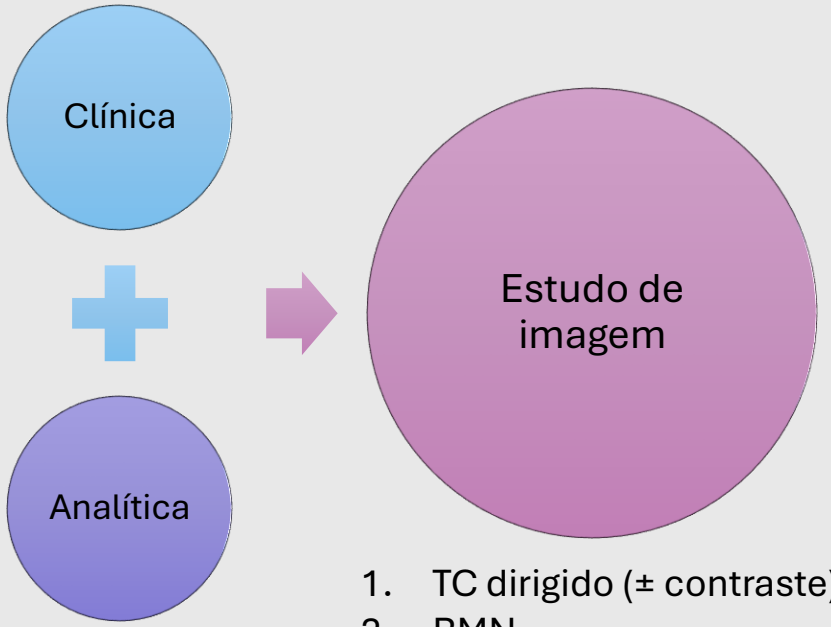
2.2 We suggest computed tomography (CT) rather than magnetic resonance imaging (MRI) as the first-choice imaging modality because of its excellent spatial resolution for thorax, abdomen, and pelvis. (**2**|⊕⊕⊕◯)

2.3 We recommend MRI in patients with metastatic PPGL, for detection of skull base and neck paragangliomas, in patients with surgical clips that cause artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, patients with known germline mutations, and those with recent excessive radiation exposure). (**1**|⊕⊕⊕◯)

2.4 We suggest the use of ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy as a functional imaging modality in patients with metastatic PPGL detected by other imaging modalities when radiotherapy using ^{131}I-MIBG is planned, and occasionally in some patients with an increased risk for metastatic disease due to large size of the primary tumor or to extra-adrenal, multifocal (except skull base and neck PPGLs), or recurrent disease. (**2**|⊕◯◯◯)

2.5 We suggest the use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT scanning in patients with metastatic disease. ^{18}F-FDG PET/CT is the preferred imaging modality over ^{123}I-MIBG scintigraphy in patients with known metastatic PPGL. (**2**|⊕⊕⊕◯)

Localização



1. TC dirigido (± contraste)
2. RMN
3. PET ^{18}F -FDOPA/ ^{68}Ga-DOTANOC

(^{123}I- MIBG atualmente menos valioso)

Lenders JW, et alJr; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42. doi: 10.1210/jc.2014-1498. Erratum in: J Clin Endocrinol Metab. 2023 Apr 13;108(5):e200. doi: 10.1210/clinem/dgad064

Casos Clínicos

Caso clínico 1

60-65 anos
Empresário

DPOC
Tabagismo ativo
Enxaqueca

Zolmitriprano 2,5 mg SOS
Atorvastatina 20 mg id
Brometo de Umeclidínio

Fev/2022

- Observado por Cirurgia Geral, por incidentalomas da suprarrenal bilaterais (identificados em TC Tórax para avaliação estrutural do pulmão)
- Sem clínica compatível com excesso de secreção hormonal
- TC dirigido a SR: “Discreto espessamento nodular de baixa densidade no braço externo da SR direita, com cerca de 10 mm, representando provável adenoma. Nódulo no braço interno da SR esquerda, medindo cerca de 24x20 mm, compatível com mielolipoma”

Parâmetros	Valor	Valor de referência
DHEA-S	48,9 µg/dL	80-560
Cortisol	19,0 µg/dL	6,2-19,4
Renina	12,06 pg/mL	2,14-53,83
Aldosterona	169,82 pg/mL	14,21-156,47
RAR		
Adrenalina		
Noradrenalina		

DHEA-S: Sulfato de Dehidroepian

Pedido de consulta de Endocrinologia

60-65 anos
Empresário

DPOC
Tabagismo ativo
Enxaquexa

Zolmitriprano 2,5 mg SOS
Atorvastatina 20 mg id
Brometo de Umeclidínio

Jan/2023

- CE Endocrinologia- confirmada ausência de clínica

Parâmetros		Valor	Valor de referência
Cortisol (Pós PFN)		2,1 µg/dL	<1,8
Plasma	Metanefrina	441 pmol/L	<456,3
	Normetanefrina	876 pmol/L	<982,8
Urina 24h	Metanefrina	1227 nmol/d	264-1729
	Normetanefrina	1586 nmol/d	480-2424
	3-Metoxitiramina	1374 nmol/d	0-1830
	Ácido vanilmandélico	4,4 mg/d	1,4-6,5

PFN: Prova de Frenação Noturna

Abril/2024

- Repetiu TC dirigido a SR para avaliar evolução dimensional, com estabilidade.

Adenoma da SR direita + Mielolipoma da SR esquerda
MACS (*mild autonomous cortisol secretion*)→ Controlo de risco cardiovascular em médico assistente

60-65 anos
Empresário

DPOC
Tabagismo ativo
Enxaquexa

Zolmitriprano 2,5 mg SOS
Atorvastatina 20 mg id
Brometo de Umeclidínio

Na presença de indicação clínica, no *workup* diagnóstico de incidentalomas suprarrenais, o rastreio bioquímico deve incluir **metanefrinas e não catecolaminas plasmáticas**, pela sua maior sensibilidade

Lenders JW, et al.Jr; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42. doi: 10.1210/jc.2014-1498. Erratum in: J Clin Endocrinol Metab. 2023 Apr 13;108(5):e200. doi: 10.1210/clinem/dgad064. PMID: 24893135.

Caso clínico 2

55-60 anos
Advogada

Neuropatia do trigémio
Perturbação de ansiedade generalizada
Hemitiroidectomia por BMN (2022)

Duloxetina 60 mg id
Carbamezepina 400 mg tid
Lisinopril 5 mg id
Bisoprolol 2,5 mg id
Rosuvastatina 5 mg id
Alprazolam 0,5 mg SOS

Fev/2025

- Referenciada a consulta de Endocrinologia por ”sintomatologia compatível com feocromocitoma com crises de taquicardia+ sensação da cabeça oca + flushing”, → acescenta em consulta sensação de corpo estranho na garganta aquando de episódios
- Do estudo prévio:

Parâmetros		Valor	Valor de referência
Plasma	Metanefrina	124 pmol/L	<456,3
	Normetanefrina	617 pmol/L	<982,8
Urina 24h	Metanefrina	506 nmol/d	264-1729
	Normetanefrina	**3219 nmol/d**	480-2424
	3-Metoxitiramina	**2001 nmol/d**	0-1830
	Ácido vanilmandélico	3,6 mg/d	1,4-6,5

- Flushing
- Sensação de dificuldade na deglutição- lobo faríngeo?
- Elevação ligeira da Normetanefrina e 3-metoxitiramina

55-60 anos
Advogada

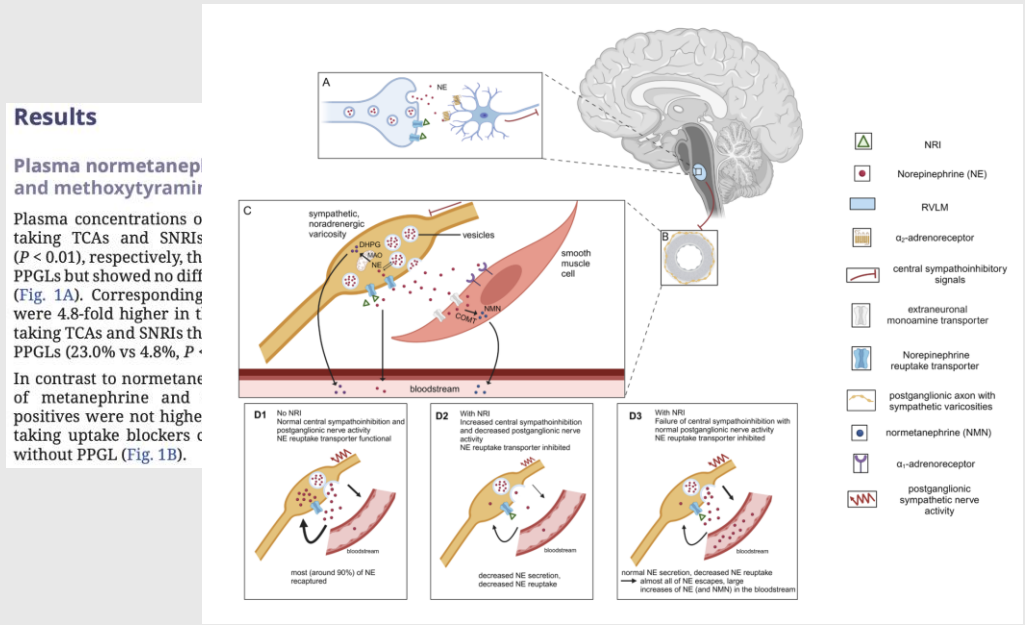
Neuropatia do trigémio
Perturbação de ansiedade generalizada
Hemitiroidectomia por BMN (2022)

Duloxetina 60 mg id
Carbamezepina 400 mg tid
Lisinopril 5 mg id
Bisoprolol 2,5 mg id
Rosuvastatina 5 mg id
Alprazolam 0,5 mg SOS

Ago/2025

- **TC dirigido a SR:** sem alterações de relevo
- Repetiu doseamento de metanefrinas, com elevação da mesma magnitude

"Duloxetine is a potent inhibitor of neuronal serotonina and norepinephrine reuptake and a weak inhibitor of dopamine reuptake" (Jaberpreet S, 2023)



Schürfeld R, Pamporaki C, Peitzsch M, Rayes N, Sabri O, Rohm S, Biemann R, Sandner B, Tönjes A, Eisenhofer G. False-positive results for pheochromocytoma associated with norepinephrine reuptake blockade. Endocr Relat Cancer. 2023 Dec 1;31(1):e230063. doi: 10.1530/ERC-23-0063.

55-60 anos
Advogada

Neuropatia do trigémio
Perturbação de ansiedade generalizada
Hemitiroidectomia por BMN (2022)

Duloxetina 60 mg id
Carbamezepina 400 mg tid
Lisinopril 5 mg id
Bisoprolol 2,5 mg id
Rosuvastatina 5 mg id
Alprazolam 0,5 mg SOS

2026

- Sintomatologia não compatível com Feocromocitoma/Paraganglioma.
- Terapêutica ajustada apoio de Neurologia e Consulta de Dor, com **suspensão de Duloxetina**

Parâmetros		Valor	Valor de referência
Plasma	Metanefrina	134 pmol/L	<456,3
	Normetanefrina	716 pmol/L	<982,8
Urina 24h	Metanefrina	254 nmol/d	264-1729
	Normetanefrina	1932 nmol/d	480-2424
	3-Metoxitiramina	830 nmol/d	0-1830
	Ácido vanilmandélico	3,8 mg/d	1,4-6,5

Elevação isolada de Normetanefrina no contexto de Duloxetina

58 anos
Advogada

Neuropatia do trigémio
Perturbação de ansiedade generalizada
Hemitiroidectomia por BMN (2022)

Duloxetina 60 mg id
Carbamezepina 400 mg tid
Lisinopril 5 mg id
Bisoprolol 2,5 mg id
Rosuvastatina 5 mg id
Alprazolam 0,5 mg SOS

Elevações persistentes ligeiras de normetanefrina devem ser interpretadas à luz da medicação concomitante, sendo os **inibidores da recaptação da noradrenalina uma causa frequente de falsos positivos**

Schürfeld R, Pamporaki C, Peitzsch M, Rayes N, Sabri O, Rohm S, Biemann R, Sandner B, Tönjes A, Eisenhofer G. False-positive results for pheochromocytoma associated with norepinephrine reuptake blockade. Endocr Relat Cancer. 2023 Dec 1;31(1):e230063. doi: 10.1530/ERC-23-0063.

Caso clínico 3

65-70 anos
Reformado. Ex operário fabril

DRC G5d (etiologia indet.)
Hepatopatia crónica
Dislipidemia
DM tipo 2
Cardiopatia hipertensiva+ valvular (Eao moderada)

Ramipril 2,5 mg id
Furosemida 120 mg bid
Bisoprolol 2,5 mg id
Pantoprazol 40 mg id
Sitagliptina 25 mg id
Atorvastatina 20 mg

Jan/2023

- Referenciado da CE Nefrologia por achado em TC abdominopélvico com “imagem nodular na SR esquerda, com 24 mm e densidade compatível com adenoma”, tendo inclusive realizado já RMN dirigida com confirmação de imagem compatível com adenoma
- Sem clínica compatível com excesso de secreção hormonal . Perfil tensional controlado.
- Pedida avaliação

Parâmetros		Valor	Valor de referência
Renina		2.7 pg/mL	2,14-53,83
Aldosterona		7 pg/mL	14,21-156,47
Cortisol (pós PFN)		2,5 µg/dL	<1,8
Plasma	Metanefrina	**2099 pmol/L**	**<456,3**
	Normetanefrina	760 pmol/L	<982,8
Urina 24h (600 mL)	Metanefrina	181 nmol/d	264-1729
	Normetanefrina	945 nmol/d	480-2424
	3-Metoxitiramina	69 nmol/d	0-1830
	Ácido vanilmandélico	3,5 mg/d	1,4-6,5

65-70 anos
Reformado. Ex operário fabril

DRC G5d (etiologia indet.)
Hepatopatia crónica
Dislipidemia
DM tipo 2
Cardiopatia hipertensiva+ valvular (Eao moderada)

Ramipril 2,5 mg id
Furosemida 120 mg bid
Bisoprolol 2,5 mg id
Pantoprazol 40 mg id
Sitagliptina 25 mg id
Atorvastatina 20 mg

Ago/2023

- Totalmente assintomático
- Repete estudo

Parâmetros		Valor	Valor de referência
Plasma	Metanefrina	509 pmol/L	<456,3
	Normetanefrina	4376 pmol/L	<982,8

Plasma metanephrines in renal failure

GRAEME EISENHOFER, FRANS HUYSMANS, KAREL PACAK, MACCLELLAN M. WALTHER,

OPEN **Optimized procedures for testing plasma metanephrines in patients on hemodialysis**

Christina Pamporaki[1✉], Aleksander Prejbisz[2], Robert Małecki[3], Frank Pistrosch[4], Mirko Peitzsch[5], Steffen Bishoff[6], Petra Mueller[6], Iris Meyer[7], Doreen Reimann[8], Katarzyna Hanus[2], Andrzej Januszewicz[2], Stefan R. Bornstein[1], Simon Parmentier[1], Carola Kunath[5], Jacques W. M. Lenders[1,9], Graeme Eisenhofer[1,5] & Jens Passauer[1]

Dan A. Niculescu, MD, PhD[1]; Gener Ismail, MD, PhD[2]; Catalina Poiana, MD, PhD[1]

"The lower plasma concentrations of metanephrines, both in venous and shunt blood, near the end rather than before starting HD indicate the former time point as preferable to minimize false positive results." (Pamporaki C et al, 2021)

Eisenhofer G, et al Plasma metanephrines in renal failure. Kidney Int. 2005 Feb;67(2):668-77. doi: 10.1111/j.1523-1755.2005.67123.x.
Niculescu DA, etal. Plasma free metanephrine and normetanephrine levels are increased in patients with chronic kidney disease. Endocr Pract. 2014 Feb;. doi: 10.4158/EP13251
Pamporaki C, et al. Optimized procedures for testing plasma metanephrines in patients on hemodialysis. Sci Rep. 2021 Jul 19;11(1):14706. doi: 10.1038/s41598-021-94104-9.

65-70 anos
Reformado. Ex operário fabril

DRC G5d (etiologia indet.)
Hepatopatia crónica
Dislipidemia
DM tipo 2
Cardiopatia hipertensiva+ valvular (Eao moderada)

Ramipril 2,5 mg id
Furosemida 120 mg bid
Bisoprolol 2,5 mg id
Pantoprazol 40 mg id
Sitagliptina 25 mg id
Atorvastatina 20 mg

Nov/2023

- Colhe estudo analítico no final da Hemodiálise, em H. Dia Endocrinologia

Parâmetros		Valor	Valor de referência
Plasma	Metanefrina	454 pmol/L	<456,3
	Normetanefrina	1031 pmol/L	<982,8

Adenoma não produtor da SR esquerda

65-70 anos
Reformado. Ex operário fabril

DRC G5d (etiologia indet.)
Hepatopatia crónica
Dislipidemia
DM tipo 2
Cardiopatia hipertensiva+ valvular (Eao moderada)

Ramipril 2,5 mg id
Furosemida 120 mg bid
Bisoprolol 2,5 mg id
Pantoprazol 40 mg id
Sitagliptina 25 mg id
Atorvastatina 20 mg

Na doença renal crónica avançada, a elevação de metanefrinas pode refletir a **redução da depuração dos metabolitos**, com contributo do aumento da atividade simpática associada à uremia.

O momento da colheita é essencial → amostras obtidas do acesso vascular **próximo ao final da sessão de hemodiálise** apresentam valores mais baixos de metanefrinas, com menor risco de falsos positivos

Eisenhofer G, et al Plasma metanephrines in renal failure. Kidney Int. 2005 Feb;67(2):668-77. doi: 10.1111/j.1523-1755.2005.67123.x.
Niculescu DA, etal. Plasma free metanephrine and normetanephrine levels are increased in patients with chronic kidney disease. Endocr Pract. 2014 Feb;. doi: 10.4158/EP13251
Pamporaki C, et al. Optimized procedures for testing plasma metanephrines in patients on hemodialysis. Sci Rep. 2021 Jul 19;11(1):14706. doi: 10.1038/s41598-021-94104-9.

Caso clínico 4

70-75 anos
Reformada

Dislipidemia mista
AIT (2014)
Catarata bilateral
POAD

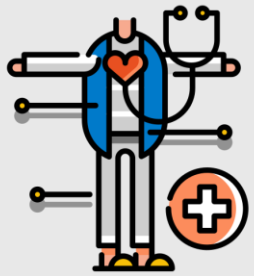
Beta-histina 24 mg bid
Omepazol 20 mg id
Atorvastatina 20 mg id
AAS 150 mg id
Alprazolam 1 mg id

Out/2025

- Referenciada da consulta de Cirurgia Geral de CHTMAD, onde era seguida após episódio isolado de dor abdominal na FIE não esclarecida

Do estudo prévio:

- TC-AP (2024): "Na dependência da SR esquerda, identifica-se um nódulo sólido, denso, bem delimitado com 34x31x29 mm, sem evidência de calcificações"
- Elevação da Metanefrina (1,3xLSN) e **Normetanefrina (9,3x LSN)** plasmáticas



S

- Episódios com **cefaleia e vertigem**→ associa a alteração posicional da cabeça. Ocasionalmente pico hipertensivo e palidez da face durante estes.
- **Mais cansada** no último ano, mas globalmente sentir-se bem

O

Fácies incaracterístico
TA:155/85 mmHg | FC: 55 bpm
Peso:76,2 kg | Altura:1,53 m | IMC:32,6 kg/m^2

70-75 anos
Reformada

Dislipidemia mista
AIT (2014)
Catarata bilateral
POAD

Beta-histina 24 mg bid
Omepazol 20 mg id
Atorvastatina 20 mg id
AAS 150 mg id
Alprazolam 1 mg id

Nov/2025

- TC dirigido a SR: " formação nodular sólida, com contornos regulares, medindo 40 mm de maior eixo axial (...) **comportamento densitométrico atípico (54 HU)**, com realce em fase venosa e ausência de lacagem significativa em fase tardia"

Parâmetros		Valor	Valor de referência
Plasma	Metanefrina	**6378 pmol/L**	<456,3
	Normetanefrina	**9487 pmol/L**	<982,8
Urina 24h	Metanefrina	**14956 nmol/d**	264-1729
	Normetanefrina	**15501 nmol/d**	480-2424
	3-Metoxitiramina	854 nmol/d	0-1830
	Ácido vanilmandélico	**12,8 mg/d**	1,4-6,5

"Older patients had a higher rate of incidental tumors, fewer typical catecholamine-related symptoms, lower plasma normetanephrine levels and higher proportion exceeding the normal glycemic range (compared to younger patients." (Xu X et al, 2025)

Xu X, Shen Y, Jiang J, Pang Y, Cheng K, Li Z, Wang Y, Chen J, Yu A, Wang J, Li M, Zhang J, Liu L. Clinical and genetic features of older patients with pheochromocytomas and paragangliomas: A multicenter retrospective study. J Endocrinol Invest. 2026 Jan;49(1):81-91. doi: 10.1007/s40618-025-02689-z. Epub 2025 Aug 20. PMID: 40833586.

70-75 anos
Reformada

Dislipidemia mista
AIT (2014)
Catarata bilateral
POAD

Beta-histina 24 mg bid
Omepazol 20 mg id
Atorvastatina 20 mg id
AAS 150 mg id
Alprazolam 1 mg id

Iniciou bloqueio alfa-adrenérgico a 20/11/2025

Jan/2026

- Submetida a adrenalectomia esquerda, sem intercorrências

Feocromocitoma

70-75 anos
Reformada

Dislipidemia mista
AIT (2014)
Catarata bilateral
POAD

Beta-histina 24 mg bid
Omepazol 20 mg id
Atorvastatina 20 mg id
AAS 150 mg id
Alprazolam 1 mg id

O feocromocitoma pode ser **paucissintomático no doente idoso**, pelo que a ausência de clínica exuberante não exclui doença clinicamente relevante.

Xu X, Shen Y, Jiang J, Pang Y, Cheng K, Li Z, Wang Y, Chen J, Yu A, Wang J, Li M, Zhang J, Liu L. Clinical and genetic features of older patients with pheochromocytomas and paragangliomas: A multicenter retrospective study. J Endocrinol Invest. 2026 Jan;49(1):81-91. doi: 10.1007/s40618-025-02689-z. Epub 2025 Aug 20. PMID: 40833586.

Mensagens Finais

- O doseamento de **metanefrinas livres plasmáticas ou urinárias fraccionadas é o teste de primeira linha** no estudo de tumores secretores de catecolaminas, sendo superior à medição direta de catecolaminas, pela sua maior sensibilidade e menor variabilidade biológica.
- Na interpretação dos resultados devemos sempre ter em atenção os **fatores pré-analíticos**, o **contexto clínico** e o **método analítico utilizado**, sob pena de falsos positivos clinicamente relevantes.
- **Elevações ligeiras ou moderadas**, sobretudo isoladas da normetanefrina, são frequentemente explicadas por **interferência farmacológica**, **stress fisiológico ou comorbilidades**.
- Fármacos que bloqueiam a recaptação da noradrenalina, nomeadamente **SNRIs e antidepressivos tricíclicos**, constituem uma **causa comum de resultados falsamente positivos** e devem ser sistematicamente considerados.
- Na **doença renal crónica avançada**, a elevação de metanefrinas pode refletir **redução da depuração dos metabolitos**, exigindo uma interpretação cautelosa.
- O feocromocitoma **pode ser paucissintomático**, particularmente em doentes idosos → **a ausência de clínica exuberante não exclui doença**, sobretudo perante elevações francas e consistentes.
- Em suma, o diagnóstico correto do feocromocitoma/paraganglioma não depende apenas do valor absoluto, mas da **integração crítica entre bioquímica, contexto clínico e imagem.**